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MORTALITY IN DIABETIC COMA

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Mortality statistics of diabetic coma at the Los Angeles County General Hospital are here presented and analyzed in an attempt to evaluate the importance of the various factors which influence the mortality of such coma.

The data were compiled from all consecutive cases of diabetic coma encountered in this hospital from 1930 through 1940. Included were only those cases in which were present (1) an elevated level of blood sugar, (2) a low carbon dioxide–combining power and (3) clinical symptoms of diabetic coma, with definite signs of mental depression. This series totaled 315 cases of coma in 274 diabetic patients. Coma occurred twice in 16 patients, three times in 5 patients, four times in 1 patient and seven times in 2 patients.

GROSS MORTALITY STATISTICS

As has been emphasized by many observers,[1] the gross mortality of diabetic coma has little comparative value, since so many variable factors are involved in determining the severity of coma in an individual patient. No 2 cases or series of cases can be directly compared unless they represent attacks of approximately equal severity.

Table 1 presents gross mortality statistics from six series of cases. Since the cases in the various series do not necessarily represent episodes

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1. (*a*) Baker, T. W.: Clinical Survey of One Hundred and Eight Consecutive Cases of Diabetic Coma, Arch. Int. Med. **58**:373-406 (Sept.) 1936. (*b*) Joslin, E. P.; Root, H. F.; White, P.; Marble, A., and Joslin, A. P.: Diabetic Coma, ibid. **59**:175-195 (Feb.) 1937. (*c*) Dillon, E. S., and Dyer, W. W.: Factors Influencing the Prognosis in Diabetic Coma, Ann. Int. Med. **11**:602-617, 1937. (*d*) Rabinowitch, I. M.; Fowler, A. F., and Bensley, E. H.: Diabetic Coma, ibid. **12**:1403-1428, 1939. (*e*) Owens, L. B., and Rockwern, S. S.: Prognosis in Diabetic Coma: Basic Importance of Mental State, Am. J. M. Sc. **198**:252-260, 1939.

of equal severity, these gross statistics are of little value in indicating success in treatment. The purpose of this study is to determine what variables are important in estimating the severity of coma and to derive a method for directly comparing cases under identical conditions.

PRECIPITATING FACTORS

The factors which could be considered responsible for precipitating the attacks of coma in this series of cases were studied. The precipitating

TABLE 1.—*Gross Mortality Statistics*

Hospital	No. of Cases	No. of Deaths	Mortality, %
Mayo Clinic (1936)[1a]	108	17	15.7
New England Deaconess Hospital (1937)[1b]	318	38	11.9
Philadelphia General Hospital (1937)[1c]	268	117	43.7
Montreal General Hospital (1939)[1d]	125	33	26.4
Cincinnati General Hospital (1939)[1e]	92	47	51.0
Los Angeles County General Hospital (1940)	315	105	33.3

TABLE 2.—*Precipitating Factors* *

A. Infections			182 (54.0%)
1. Infection of the respiratory tract		105	
(*a*) Infection of the upper respiratory tract	64		
(*b*) Pneumonia	27		
(*c*) Tuberculosis	7		
(*d*) Otitis media	7		
2. Acute gastrointestinal upsets		28	
3. Subcutaneous abscesses, etc.		24	
4. Foot infections, gangrene		12	
5. Pyelitis, pyelonephritis		6	
6. Miscellaneous		7	
B. Dietary infractions or omission of insulin			77 (22.6%)
1. Insufficient insulin		43	
2. Dietary indiscretions (?)		18	
3. No treatment prior to coma		16	
C. Miscellaneous factors			14 (4.1%)
D. No recorded factor			64 (19.0%)

* Twenty-two cases in which the patients were in diabetic acidosis but were mentally alert were included in this table only.

factor in a case of diabetic coma was considered to be a definite recent illness, a disturbance in a patient's dietary or insulin regimen or other immediate unusual event in his history, with subsequent appearance of symptoms of coma.

As shown in table 2, in 54 per cent of all cases coma was precipitated by infections, the great majority of which affected the respiratory tract.

Insulin insufficiency was the second most common precipitating factor of coma, due either to complete cessation of insulin or administration of sufficient doses.

Acute gastrointestinal upsets included dysenteries, food poisonings, etc., but in many cases it was difficult to determine whether a gastrointestinal upset precipitated the coma or whether it was the first symptom of coma.

Dietary indiscretion as the precipitating agent was probably not as important a factor as the table would indicate. Careful study of the histories in each of the 18 cases so classified proved it difficult to determine whether pure dietary or carbohydrate excess was the primary causative agent. In 4 cases the onset of coma was associated with acute alcoholism. In the remaining ones the history was not incompatible with mild food poisoning, acute gastritis or simple acute gastrointestinal upset. The question of associated insufficient insulin dosage as a contributing factor could not be ruled out in many instances. Critical analysis indicated that although in the 18 cases coma was precipitated by unusual or excessive food intake, in none could it be

TABLE 3.—*Time of Death*

After entry.....	1 Hr.	2-5 Hr.	6-12 Hr.	13-24 Hr.	25-36 Hr.	37-48 Hr.	49-72 Hr.	73-96 Hr.	5-7 Days	8-14 Days
Number of deaths.....	4	11	24	24	13	8	6	5	2	3

directly attributed to pure carbohydrate excess. It has been the contention of Mirsky and co-workers [2] that excessive carbohydrate ingestion is not a precipitating cause for diabetic coma.

Coma was the mode of onset of diabetes in 16 cases. Five per cent of comas occurred in patients who were unaware of previous diabetes.

Foot infections and gangrene as the precipitating factors occurred predominantly in the older age groups.

TIME OF DEATH AFTER ADMISSION TO HOSPITAL

How soon a patient died after admission to the hospital tends to indicate to some degree the severity of coma on admission. It is noted in table 3 that 48 per cent of fatalities occurred six to twenty-four hours after entry into the hospital. Four per cent of deaths occurred within one hour after admission, the condition obviously being terminal on entry. Five per cent of deaths occurred after four days from complications, not from diabetic coma per se.

2. Mirsky, I. A.; Franzblau, A. N.; Nelson, N., and Nelson, W. E.: Role of Excessive Carbohydrate Intake in the Etiology of Diabetic Coma, J. Clin. Endocrinol. **1**:307-315, 1941.

CHRONOLOGIC DISTRIBUTION

Table 4 presents the percentage mortality of diabetic coma according to years. It is noted that the average percentage mortality in all cases from 1930 through 1934 was 41.7 per cent. During this period patients in diabetic coma were admitted to various wards throughout the hospital. In May 1934 two wards for diabetic patients were inaugurated, and all such patients have since been segregated in these wards, under

TABLE 4.—*Chronologic Distribution*

Year	No. of Cases	No. of Deaths	Mortality, %
1930	15	8	53.3
1931	12	3	25.0
1932	27	9	33.3
1933	41	19	46.3
1934	8	4	50.0
1930-1934	103	43	41.7
1935	18	4	22.2
1936	27	7	25.9
1937	37	13	35.1
1938	42	16	38.1
1939	44	12	27.3
1940	44	10	22.7
1935-1940	212	62	28.3
1930-1940	315	105	33.3

TABLE 5.—*Seasonal Distribution*

Month	Number of Cases	Number of Deaths	Mortality, %	Infections
January	28	8	29.6	14
February	26	11	42.3	12
March	24	10	41.6	14
April	25	11	44.0	15
May	21	7	33.3	8
June	20	6	30.0	10
July	32	9	28.1	14
August	23	6	26.1	13
September	29	6	20.7	12
October	30	11	36.7	15
November	22	9	40.8	9
December	35	10	28.8	18

the supervision of attending and resident physicians especially interested in diabetes mellitus. Probably as a result of this specialized care, the average percentage mortality from 1935 through 1940 was 28.3 per cent. The gross average mortality in 315 cases of diabetic coma from 1930 through 1940 was 33.3 per cent.

SEASONAL DISTRIBUTION

A study of the cases according to the month in which the patients were admitted for coma revealed (table 5) that their distribution throughout the twelve months was quite uniform, the greatest incidence

being in December. Baker [1a] and Joslin and associates [3] have found coma to be most frequent in August. When the cases with associated infection were plotted by months (table 5), the greatest incidence of infection was also found to be in December. There was a close relation between incidence of coma and incidence of associated infection.

A striking variation of mortality with season was also demonstrated in table 5. A low mortality of about 29 per cent occurred in December and January, rising to a high of 44 per cent in April, then decreasing to a second low of 20.7 per cent in September and again rapidly rising to a second high peak of 40.8 per cent in November. The two high peaks of mortality in spring and late fall are clearly shown in figure 1. Although it was observed that a close relation existed between monthly incidence of coma and associated infection, no relation was noted between monthly incidence of infection in diabetic coma and mortality. Likewise,

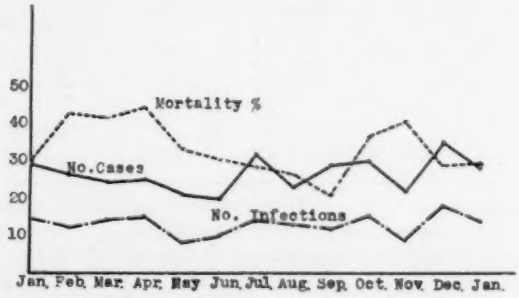


Fig. 1.—Monthly distribution of mortality of diabetic coma, incidence of coma and incidence of infections in 315 cases of diabetic coma.

study of the original data revealed that the number of deaths in each individual month was evenly distributed throughout the years, so that the peak in November, for example, was not due to an epidemic of deaths in any one year.

RELATION OF MORTALITY TO SEX

As shown in table 6 the average mortality for the two sexes was equal. It is interesting to note that in almost two thirds of the cases of coma the patients were women; this greater frequency has also been demonstrated by other observers.[1]

Owens [1e] stated that coma occurs more frequently during the decade of puberty and of menopause, with higher mortality in the female in

3. Joslin, E. P.; Root, H. F.; White, P.; Marble, A., and Hunt, H. M.: Diabetic Coma, M. Clin. North America **16**:793-827, 1933.

these periods. Table 6 confirms the observation that coma apparently was more prone to occur during the puberal and the climacteric period, but mortality was not higher in the female.

RELATION OF MORTALITY TO AGE

The oldest patient was an 85 year old woman, who died of complicating empyema of the gallbladder and pneumonia. The oldest patient to recover was a 75 year old man whose blood contained 832 mg. of sugar per hundred cubic centimeters and had a carbon dioxide–combining power of 13 volumes per cent. The youngest patient was 6 years old.

TABLE 6.—*Interrelation of Sex, Age and Mortality*

	Males			Females		
Age, Yr.	Number of Cases	Number of Deaths	Mortality, %	Number of Cases	Number of Deaths	Mortality, %
0-9	6	1	16.6	6	2	33.3
10-19	21	3	14.3	44	2	4.5
20-29	22	6	27.3	30	9	30.0
30-39	18	4	22.2	25	7	28.0
40-49	25	11	44.0	33	12	36.4
50-59	14	7	50.0	28	17	60.8
60-69	6	4	66.6	22	8	36.3
70+	6	4	66.6	9	8	89.0
Total	118	40	33.9	197	65	33.0

TABLE 7.—*Relation of Mortality to Age*

Age, Yr.	Number of Cases	Number of Deaths	Mortality, %
—15	46	6	13.0
16-30	85	14	16.5
31-50	105	41	39.0
51-70	65	33	50.7
71+	14	11	78.6

The largest group of cases represented patients between 30 and 50 years of age.

Table 7 shows the relation of mortality to the age of a patient. As the age of the patient increases, the mortality increases in a direct relation. Patients 80 years of age had roughly about twice the mortality of patients 40 years of age, who in turn had approximately twice the mortality of patients 20 years of age. The age of the patient, therefore, is obviously an important factor in influencing the severity of diabetic coma.

RELATION OF MORTALITY TO DURATION OF COMA

The length of time a patient had been in coma was not always definite but was estimated from the time at which the patient definitely

became drowsy. The longest duration of coma before admission to the hospital was ninety-six hours, as observed in 6 cases. The duration of coma is usually considered an important factor in determining the prognosis, and table 8 indicates that this is true to a certain degree; however, previous observers have not analyzed the relation in adequately small periods over a sufficient time. It was noted that the mortality rose rapidly as duration of coma approached twenty-four hours, then reached a plateau from twenty-five to forty-eight hours, after which the percentage mortality actually dropped. As has been demonstrated elsewhere,[4] untreated patients in coma and still alive after forty-eight hours not only had a lower average mortality, but had a less severe degree of acidosis.

TABLE 8.—*Relation of Mortality to Duration of Coma*

Hours	Number of Cases	Number of Deaths	Mortality, %
—12	184	43	23.4
13-24	62	26	41.9
25-36	2	1	50.0
37-48	17	9	53.0
49+	15	5	33.3
Unknown	35		

TABLE 9.—*Relation of Mortality to Degree of Unconsciousness*

Degree of Unconsciousness	Number of Cases	Number of Deaths	Mortality, %
Drowsy	85	5	5.9
Semiconscious	93	20	21.5
Unconscious (responds to painful stimuli)	106	54	51.0
Completely unconscious	31	26	83.8

RELATION OF MORTALITY TO DEGREE OF UNCONSCIOUSNESS

Table 9 shows that as the degree of mental depression increased, the mortality increased proportionately. Patients admitted in uncomplicated diabetic "coma" who were alert and conscious had a mortality of zero in this hospital. As has been emphasized by Rabinowitch and associates [1d] and borne out by this series of cases, alert patients in a state of diabetic acidosis should not be classified as being in coma. No case in which a patient was alert or conscious was included in this series. Patients admitted completely unconscious and not responding to painful stimuli, such as corneal touch or supraorbital pressure, had the high mortality of 83.8 per cent. Thus the degree of unconsciousness of a patient is an important factor in determining the severity of coma.

4. Collen, M. F.: Interrelation of the Factors Influencing Mortality in Diabetic Coma: A Statistical Study, Arch. Int. Med., this issue, p. 369.

RELATION OF MORTALITY TO BLOOD PRESSURE

Although it is a well known fact that the mortality of diabetic coma is closely related to blood pressure, few writers have included blood pressure among those factors of greatest importance in determining ultimate prognosis.[5] Previous attempts to estimate the importance of blood pressure in grading severity of coma have been based only on systolic blood pressure.[1d] Table 10 *A* shows that when systolic blood pressure was over 90 mm. of mercury, the average mortality was 27.6 per cent. When the systolic blood pressure fell to shock levels, i. e.,

TABLE 10.—*Relation of Mortality to Blood Pressure*

A. Systolic Blood Pressure, Mm. Hg	Number of Cases	Number of Deaths	Mortality, %
90+	210	58	27.6
80-80	18	13	72.2
79-70	7	4	57.2
69-60	2	2	100.0
59-50	4	4	100.0
49—	17	14	82.3
B. Diastolic Blood Pressure, Mm. Hg			
80+	105	25	23.8
79-70	50	13	26.0
69-60	42	13	31.0
59-50	21	12	57.1
49-40	10	8	80.0
39—	28	23	82.2
Unknown	59		
C. Pulse Pressure, Mm. Hg			
60+	49	17	34.7
59-40	83	24	28.6
39-30	50	20	30.0
29-20	27	9	33.3
19—	14	13	92.8

under 90 mm. of mercury, the mortality immediately rose to over 72.2 per cent. Groups in which the blood pressure values ranged from 79 to 50 mm. of mercury were combined because of the small number of cases. It is obvious that the systolic blood pressure is valuable only in classifying severity of coma in two kinds of patients: (1) those in shock, with an average mortality of about 75 per cent, and (2) those not in shock, with an average mortality of about 28 per cent.

Physiologically, the diastolic blood pressure is a better measure of shock than the systolic blood pressure, and table 10 *B* bears out this point. It is evident that as the diastolic blood pressure fell, the mortality

5. (*a*) Wilder, R. M.: Clinical Diabetes Mellitus and Hyperinsulinism, Philadelphia, W. B. Saunders Company, 1940. (*b*) Owens and Rockwern.[1e]

correspondingly rose in an almost direct relation. The diastolic blood pressure has a much closer quantitative relation to percentage of mortality than the systolic blood pressure and is therefore an important factor influencing the mortality of diabetic coma.

To determine whether the pulse pressure had an effect on mortality table 10 *C* was prepared. Mortality was independent of pulse pressure until the pulse pressure fell below 20 mm. of mercury to obvious shock levels; then the mortality immediately jumped from 33 to 92.8 per cent. Pulse pressure confirms and bears out the important effect of shock on mortality but is of no value as a quantitative yard stick with which to measure severity of coma.

RELATION OF MORTALITY TO BLOOD SUGAR

Although it is usually stated that the mortality of diabetic coma is not dependent on the degree of hyperglycemia, it has been shown by

TABLE 11.—*Relation of Mortality to Blood Sugar*

Sugar, Mg./100 Cc.	Number of Cases	Number of Deaths	Mortality, %
—299	25	2	8.0
300-499	99	23	23.2
500-799	136	52	38.2
800-999	36	18	50.0
1,000+	19	10	52.6

various observers [1d] that there is a definite rise in mortality with higher values of blood sugar. This is also confirmed by the present study (table 11), which shows a definite rise in mortality as blood sugar rises, leveling off at an average mortality of about 50 per cent with blood sugar values over 800 mg. per hundred cubic centimeters. The highest level of blood sugar in this series was 1,334 mg. per hundred cubic centimeters, in a patient who died in shock thirty-six hours after admission. The highest level of blood sugar in a patient who recovered was 1,332 mg. per hundred cubic centimeters, in a 12 year old boy, admitted unconscious, with duration of coma under twelve hours, no blood pressure obtainable and a carbon dioxide–combining power of the blood of 22 volumes per cent on admission. The highest value reported for blood sugar in a case of nonfatal coma was 1,850 mg. per hundred cubic centimeters.[6]

6. Dillon, E. S., and Dyer, W. W.: Diabetic Coma with Extreme Hyperglycemia, Am. J. M. Sc. **190**:683-686, 1935.

RELATION OF MORTALITY TO THE CARBON DIOXIDE–COMBINING POWER OF THE BLOOD

It has long been believed that the carbon dioxide–combining power of the blood is a measure of the severity of diabetic coma. In fact, Joslin and associates [1b] established a carbon dioxide–combining power of the plasma of 20 volumes per cent as the arbitrary dividing line between coma and precoma. However, reference to table 12 indicates that in cases in which the carbon dioxide–combining power is more than 20 volumes per cent the mortality is as high as in cases in which the carbon dioxide–combining power is 10 volumes per cent. The average mortality in all cases in which the carbon dioxide–combining power of the blood was 20 volumes per cent or over was 33.3 per cent; the average mortality in all cases in which this factor measured 19 volumes per cent or under was exactly the same, namely,

TABLE 12.—*Relation of Mortality to the Carbon Dioxide–Combining Power of the Blood*

Carbon Dioxide, Vol. %	Number of Cases	Number of Deaths	Mortality, %
20+	69	23	33.3
19-16	75	23	30.7
15-12	79	24	30.4
11-8	70	22	31.4
7-4	20	12	60.0
3—	2	1	50.0

33.3 per cent. In 69 (22 per cent of the entire series) the value for this factor was over 20 volumes per cent. On the basis of similar data, Dillon and Dyer [1c] included in their series all cases in which the carbon dioxide–combining power of the blood was 29 volumes per cent or below, and Baker [1a] included cases in which this factor measured 28 volumes per cent or below.

Rabinowitch and co-workers,[1d] citing a total of 713 cases of coma, showed conclusively that there is no relation between the carbon dioxide–combining power of the blood and mortality; in fact, they pointed out that the highest mortalities occurred in cases in which this factor was greater than 25 volumes per cent. The highest value in my series was 30 volumes per cent, in a 75 year old man, admitted without any history obtainable, completely unconscious and with a blood pressure of 80 mm. of mercury systolic and zero mm. of mercury diastolic, a blood sugar level of 715 mg. per hundred cubic centimeters and no complications; the patient died in shock six hours after admission; autopsy failed to disclose any abnormalities other than those consistent with uncomplicated diabetic coma. The lowest value for the carbon

dioxide–combining power of the blood in this series was 3 volumes per cent, in a 46 year old woman, admitted unconscious and with a blood pressure of 130 systolic and 80 diastolic measured in millimeters of mercury, a blood sugar level of 582 mg. per hundred cubic centimeters, blood nonprotein nitrogen level of 63 mg. per hundred cubic centimeters and a complicating infection of the upper respiratory tract; she responded to therapy but died two weeks later of pyelonephritis.

RELATION OF MORTALITY TO BLOOD NONPROTEIN NITROGEN

The highest value for blood nonprotein nitrogen in a case of uncomplicated diabetic coma was 156 mg. per hundred cubic centimeters, for a 48 year old woman, admitted semiconscious, in a coma of forty-eight hours' duration and with a blood pressure of 90 systolic and 60 diastolic measured in millimeters of mercury, a blood sugar level of 666 mg. per hundred cubic centimeters and a carbon dioxide–

TABLE 13.—*Relation of Mortality to Blood Nonprotein Nitrogen*

Nonprotein Nitrogen, Mg./100 Cc.	Number of Cases	Number of Deaths	Mortality, %
—40	43	9	20.9
41-60	35	13	37.1
61-80	22	13	59.0
81-100	14	7	50.0
101-120	4	3	75.0
121+	4	4	100.0
Unknown	193		

combining power of 28.6 volumes per cent; the patient died of anuria four days after admission; autopsy revealed a normal heart and normal kidneys; the diagnosis was severe azotemia due to uncomplicated diabetic coma.

Table 13 indicates a direct relation between mortality and degree of azotemia. In cases in which the value for blood nonprotein nitrogen were normal the average mortality was 20.9 per cent; in cases in which the values exceeded 121 mg. per hundred cubic centimeters the mortality was 100 per cent. Blood nonprotein nitrogen is an important factor in determining the severity of diabetic coma.

RELATION OF MORTALITY TO COMPLICATIONS

The mortality of diabetic coma rises with any complication. Table 14 *A* shows that the presence of an infection approximately doubled the mortality. On the other hand, a complication which was capable of causing death independent of the coma (table 14 *B*) more than quad-

rupled the mortality. More detailed study of the relation between complications and mortality is shown in table 14 *C*. This table includes complications of all types, in which the severity of the complication was estimated and graded from 1 (very mild) to 5 (very severe). It is evident from table 14 *C* that complications occurred in over half (56 per cent) of the cases of coma. The average mortality in cases of uncomplicated coma in this series was 22.8 per cent; that in cases of complicated coma rose in direct proportion to the severity of the complication, very severe complications (grade 5) having 90.8 per cent mortality. The two groups of cases in which complications were mild (grades 1 and 2) predominantly represented infections of the respiratory tract

TABLE 14.—*Relation of Mortality to Complications*

	Number of Cases	Number of Deaths	Mortality, %
A. Relation of Mortality to Infections			
Infection absent	163	40	24.5
Infection present	152	65	42.0
B. Relation of Mortality to Acute Associated Diseases Capable of Causing Death Independent of Coma			
Disease absent	220	37	16.8
Disease present	95	68	71.5
C. Relation of Mortality to Complications of All Types			
Severity of complication			
None	138	31	22.8
1	78	8	10.2
2	11	2	18.2
3	18	5	27.8
4	16	10	62.5
5	54	49	90.8

in younger age groups. This age factor explains the lower average mortality in groups in which complications were mild than in the group without uncomplications comprising all ages. Although the estimation of the severity of a complication is arbitrary, requiring much clinical judgment, it is evident from this series of cases that the percentage mortality is directly proportional to the severity of the complication. The presence of a complication is an important factor influencing the mortality of diabetic coma.

MISCELLANEOUS FACTORS

Patients in diabetic coma with coffee ground vomitus had an average mortality of 25 per cent in this series. The presence of hematemesis, therefore, does not have any great significance in prognosis.

Other studies[7] have shown that there is little relation between degree of leukocytosis and mortality. The great majority of patients in coma had white cell counts over 10,000 per cubic millimeter.

CAUSES OF DEATH

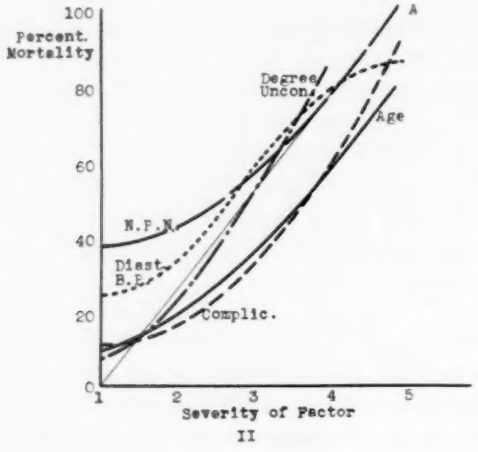
Analysis of the 105 deaths in this series revealed that in cases of uncomplicated coma 74.3 per cent of the patients died of shock. In cases of complicated coma only 36.6 per cent of the patients died of shock, while death in the remaining cases was due to associated diseases (most important of which were pneumonia 28.1 per cent, sepsis 15.5 per cent and cardiac failure 8.5 per cent). This indicates that the treatment of diabetic coma should be directed, first, toward the prevention of and treatment of shock, and, second, toward the correction of any associated disease.

ESTIMATION OF SEVERITY OF DIABETIC COMA

It has been shown that there are many factors which influence the severity of diabetic coma and the resulting mortality, namely, the age of the patient, the degree of unconsciousness, the blood pressure, the duration of coma, the blood nonprotein nitrogen, the blood sugar and the severity of complications. Theoretically, an ideal index of severity of diabetic coma would be one which would indicate that very mild forms (grade 1) would have practically zero mortality, moderately severe forms (grade 3) would have about 50 per cent mortality and very severe forms (grade 5) would have about 100 per cent mortality. In other words, there should exist a linear relation between mortality and severity index. Figure 2 demonstrates that if one grades the various factors from 1 to 5, in which grade 1 is very mild and grade 5 very severe and plot their relation to percentage mortality, using values obtained in tables 7 through 14, the factors fall into two groups. Those in figure 2 *A*, namely, the age of the patient, the degree of unconsciousness, the diastolic blood pressure, the severity of complications and the blood nonprotein nitrogen, all show almost a linear relation between the severity of the factor and the percentage mortality, approximating closely the theoretic "ideal" index. These factors obviously are important and dependable criteria for evaluating severity of coma. On the other hand, in figure 2 *B* it is evident that the systolic blood

7. Dillon and Dyer.[1c] Rabinowitch.[1d]

pressure and the carbon dioxide–combining power of the blood can have little value in indicating the severity of coma, whereas the duration of coma and the height of blood sugar may have some limited value.



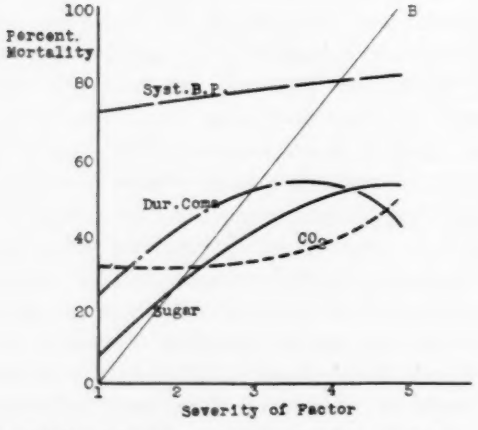


Fig. 2.—Relation between percentage mortality and the severity of various factors in diabetic coma.

DEVELOPMENT OF A SEVERITY INDEX OF DIABETIC COMA

It has been demonstrated that no single factor may be taken by itself as a reliable index of severity and prognosis in diabetic coma. For the purpose of determining a quantitative index for estimation of the

degree of severity of coma, so that mortality statistics of different series may be comparable, Rabinowitch and associates [14] developed a "severity index" based on evaluation of the several variables, as shown in table 15. Grades of severity from 1 to 5 were assigned to each variable, and the combined use of all the variables gave an index of severity which the authors demonstrated to be superior to general clinical impression and estimation of severity. Although this is a marked advancement toward proper evalution and comparison of cases, it was felt from this study that certain modifications of the Rabinowitch severity index were indicated.

In the present study age, degree of unconsciousness and blood nonprotein nitrogen all were shown to have a direct relation to mortality;

TABLE 15.—*Calculation of Severity Index (Rabinowitch)*

Factor	Rating				
	1	2	3	4	5
Age, yr.	—15	16-30	31-50	51-70	71+
Duration of coma, hr.	—12	13-24	25-36	37-48	49+
Degree of unconsciousness	Drowsy	Semi-conscious	Unconscious (but responds to pain)	.....	Completely unconscious
Coffee ground vomitus	.....	.....	Present		
Infection	.....	.....	Present		
Blood pressure, systolic, mm. Hg	89-80	79-70	69-60	59-50	49—
Carbon Dioxide-Combining power, vol. %	19-16	15-12	11-8	7-4	3—
Nonprotein nitrogen, mg. per 100 Cc.	41-60	61-80	81-100	101-120	121+
Associated conditions (acute conditions capable of causing death independent of coma)	Very mild	Mild	Moderately severe	Severe	Very severe

these factors deserve the values assigned to them. With reference to duration of coma, Rabinowitch in his analysis failed to study this factor in twelve hour periods, as presented in table 8. This table and also figure *2 B* indicate that duration of coma does not bear a direct relation to mortality, as does age, for example. A patient who has been in coma fifty hours does not deserve a rating five times that of a patient who has been in coma ten hours. Figure *2 B* shows that patients in coma over twenty-four hours have a mortality of 40 to 50 per cent; it is felt, therefore, that patients in coma over twenty-four hours deserve a grade 3 of severity but no further separation is justifiable. Patients in coma under twenty-four hours do not deserve any grade, since too much "padding" of the lower indexes of severity results.

Cases in this series in which coffee ground vomitus was present had only 25 per cent mortality; this being below average mortality for

the entire series, the presence of hematemesis does not indicate a higher mortality and does not deserve an additional grade.

It has been shown in table 10 and figure 2 *B* that diastolic blood pressure is a much more reliable index of severity than systolic blood pressure; it is therefore recommended that diastolic blood pressure be used in determining the severity index.

It has been indicated repeatedly in this discussion that the carbon dioxide–combining power of the blood has no relation to severity of coma; a patient with a value for this factor of 5 volumes per cent does not deserve a more severe grade than one with a value of 20 volumes per cent. It is concluded that there is no justification for including this factor in the calculation of the severity index.

TABLE 16.—*Modified Severity Index of Diabetic Coma*

Factor	Rating				
	1	2	3	4	5
Age, yr.	—15	16-30	31-50	51-70	71+
Diastolic blood pressure, mm. Hg	60-60	50-50	49-40	39-30	—27
Complication	Very mild	Mild	Moderately severe	Severe	Very severe
Blood nonprotein nitrogen, mg./100 cc.	41-60	61-80	81-100	101-120	121+
Degree of unconsciousness	Drowsy	Semi-conscious	Unconscious (responds to pain)	Completely unconscious	
Duration of coma, hr.			24+		
Blood sugar, mg./100 cc.			800+		

In the Rabinowitch severity index consideration is given to complications of two types, infections and acute conditions capable of causing death independent of coma. The present series of cases indicated that patients with chronic heart disease have as high a mortality as patients with other acute conditions. Serious complicating chronic diseases are as important as acute conditions in influencing mortality. An additional grade 3 because the complication is an infection is not justified, for the same condition is graded twice; e. g., a patient with moderately severe gangrene of the foot, which is secondarily infected, would receive a grade 3 for an associated condition and a grade 3 for the presence of an infection, which would give him a total grade of 6 for complicating diseases; whereas a patient with a much more severe complication of massive cerebral hemorrhage receives only a grade of 5. It is recommended that all complications be placed in one group, as has been done in this series of cases. A patient with acute follicular tonsillitis has a very mild complication and receives a grade

of 1; a patient with moderately severe gangrene of a foot receives a grade of 3, and a patient with hypertensive heart disease and evidence of congestive heart failure receives a grade of 5. Such conditions as arteriosclerosis and latent syphilis are not considered as complications.

It has been shown in table 11 and figure 2 *B* that a definite relation exists between blood sugar and mortality. Figure 2 *B* indicates that a patient with a blood sugar value over 800 mg. per hundred cubic centimeters has a mortality of over 50 per cent. Such a value then deserves an additional grade of 3.

As a result of these studies a modification of the Rabinowitch severity index is proposed and is presented in table 16.

CALCULATION OF SEVERITY INDEX

Two examples of the method by which the index of severity is calculated are given:

Example 1:

Factor	Severity	Grade
Age of patient	30 yr.	2
Diastolic blood pressure	60 mm. Hg.	1
Severity of complication	None	0
Blood nonprotein nitrogen	65 mg./100 cc.	2
Degree of unconsciousness	Semiconscious	2
Duration of coma	15 hr.	0
Blood sugar	870 mg./100 cc.	3
	Severity index	10

From figure 3 it is seen that a severity index of 10 gives this patient a prospective mortality of about 20 per cent, according to this series of cases.

Example 2:

Factor	Severity	Grade
Age of patient	60 yr.	4
Diastolic blood pressure	0 mm. Hg	5
Severity of complication	Gangrene and pneumonia	5
Blood nonprotein nitrogen	95 mg./100 cc.	3
Degree of unconsciousness	Complete	4
Duration of coma	15 hr.	0
Blood sugar	700 mg./100 cc.	0
	Severity index	21

Figure 3 shows that the prospective mortality for this patient is 98 per cent.

COMPARISON OF INDEXES

Of the entire series of cases, in only 107 were sufficient data available to calculate the severity index by the methods brought out. Table 17 presents the same 107 cases with severity indexes calculated both by the Rabinowitch and by the modified index. It is noted that the Rabinowitch index produces mortalities consistently low in the groups of cases of milder coma. There is not sufficient difference in mortality of patients with indexes below 10 to warrant separation; this is due to the "padding" of unnecessary factors in the groups of cases of milder coma and is eliminated in the modified index. This is better shown in figure 3, in which the mortality curves are plotted for both indexes.

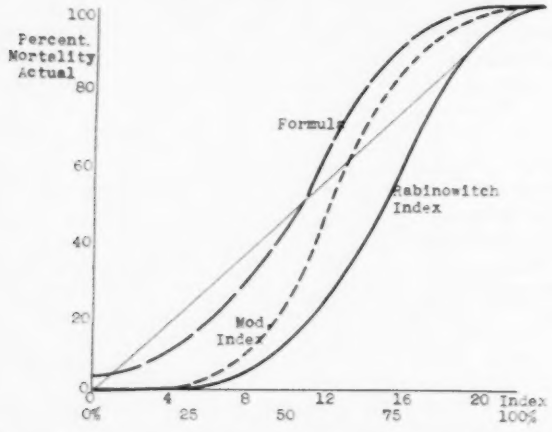


Fig. 3.—Comparison of actual mortality and calculated mortality in 107 cases of diabetic coma.

The "ideal" index would be a direct straight line relation between mortality and severity index. It is evident that the Rabinowitch index produces values too low and gives a curve which falls below the "ideal" in its entirety. The proposed modified index approaches more closely to the "ideal."

The modified severity index is recommended because (1) it is simpler, (2) it is theoretically more accurate and (3) it actually gives a more direct relation to mortality.

DERIVATION OF A SEVERITY FORMULA

Further analysis of the modified severity index and of figure 2 suggested that a mathematical formula might be obtained representing

the relation between mortality and severity, thus further simplifying calculations.

As was pointed out in discussion of figure 2*A*, there is a direct relation between mortality and (1) the age of the patient, (2) the degree of unconsciousness, (3) the diastolic blood pressure, (4) the severity of complications and (5) the blood nonprotein nitrogen. Of less importance is the relation between mortality and the blood sugar and the duration of coma. To obtain a formula of greater simplicity for practical use, it is evident that both duration of coma and blood sugar are of secondary importance in estimating mortality. It has been shown elsewhere [4] that a direct linear relation exists between blood nonprotein nitrogen and diastolic blood pressure. Because of the direct quantitative relation between the two, one may be used to represent the other; to use both factors may give too much weight to the same primary influencing factor; therefore, blood nonprotein nitrogen may be represented by diastolic blood pressure. Although there is a direct relation between age and complicating diseases, these two factors are still fundamentally independent, the direct relation being due to coincidental but constant occurrence of more frequent and severe complications in the older age groups. Both age and complicating diseases must be considered in estimating severity of coma. Therefore, one finds four "primary" fundamental factors influencing mortality, namely, (1) age, (2) diastolic blood pressure, (3) degree of unconsciousness and (4) complicating diseases. Figure 2*A* shows the relation of these four basis variables to mortality. It is seen that they all lie along the average "ideal" severity index sought and that the mean of these four curves will approach this "ideal" closely.

TABLE 17.—*Comparison of Percentage Mortality Calculated with Severity Indexes and the Severity Formula*

	Rabinowitch Index			Modified Index			Severity Formula			
		Deaths			Deaths				Deaths	
Index	No. of Cases	No.	%	No. of Cases	No.	%	Formula, %	No. of Cases	No.	%
−5	2	0	0.0	12	0	0.0	−20	28	4	14.3
6-10	28	1	3.6	41	4	9.8	21-40	38	7	18.5
11-15	36	10	27.8	29	17	58.5	41-60	16	8	50.0
16-21	34	25	73.5	21	18	85.6	61-80	21	19	90.0
21+	7	7	100.0	4	4	100.0	81+	4	4	100.0

The curve of mortality versus age is closely approximated by a direct proportion:

(*a*) mortality = age

The curve of mortality versus diastolic blood pressure is approximated by:

(*b*) mortality = 100 diastolic blood pressure

The curve of mortality versus degree of unconsciousness is approximated by:

$$(c)\ \text{mortality} = 30\ (\text{degree of unconsciousness}) - 25$$

in which the degree of unconsciousness is graded from 1 to 4.

The curve of mortality versus complicating diseases has been similarly approximated to simplify the final formula:

$$(d)\ \text{mortality} = 30\ (\text{severity of complication}) - 25$$

in which the severity of the complication is graded from 1 to 5.

Adding formulas (a), (b), (c) and (d) and dividing by 4 to obtain an average composition formula representing all these factors, one obtains:

$$\text{Mort. \%} = \frac{30\ (\text{Uncon.}) - 25 + 30\ (\text{Comp.}) - 25 + \text{Age} + 100 - \text{D.B.P.}}{4}$$

By simplifying one obtains:

$$\text{Mort. \%} = \frac{30\ (\text{Uncon.} + \text{Comp.}) + \text{Age} + 50 - \text{D.B.P.}}{4}$$

in which

Mort. % = predicted average percentage mortality
Uncon. = degree of unconsciousness (graded 1 to 4)
Comp. = severity of complication (graded 1 to 5)
Age = age of patient (years)
D.B.P. = diastolic blood pressure (mm. mercury)

By the use of this formula, one obtains a direct value in percentage which is equivalent to the average percentage mortality which a patient has according to this series of statistics.

For example, a 30 year old patient admitted semiconscious (grade 2), with a diastolic blood pressure of 60 mm. of mercury and no complicating diseases, has a prospective mortality of:

$$\text{Mort. \%} = \frac{30\ (2 + 0) + 30 + 50 - 60}{4} = 20\%$$

From simple examination of this patient and use of this formula it is quickly determined that the prospective mortality of this patient is 20 per cent; i. e., he has one out of five chances of dying of coma.

Again for example, a 60 year old patient is admitted completely unconscious (grade 4), with no blood pressure obtainable and with gangrene of one foot and lobar pneumonia (grade 5 complication). The prospective mortality of this patient is:

$$\text{Mort. \%} = \frac{30\ (4 + 5) + 60 + 50 - 0}{4} = 95\%$$

To indicate the accuracy of this formula, it was applied in the same 107 cases listed in table 17 and actual mortality was compared

to predicted mortality. For comparison of the formula with the severity indexes the cases were separated into five groups of 20 per cent each, groups which are actually too large to indicate the true accuracy of the formula. In figure 3 the actual mortality is plotted against predicted mortality by use of the formula; along the ordinate is plotted the actual mortality, and along the lower abscissa is plotted the mortality calculated by the severity formula for the same 107 cases. It is apparent that the formula as an index is superior to the Rabinowitch index and even closer to the "ideal" than the modified index. The fact that the actual mortality is slightly higher than the calculated mortality in the most severe coma is an advantage rather than a disadvantage, since improved methods of treatment will tend to lower the actual mortality and the actual and the calculated mortality will approach one another.

The formula indicates that although chemical values of the blood are indispensable in following the treatment of coma and in indicating the severity of acidosis, they are not necessary in estimating mortality in diabetic coma. Other writers [8] are in agreement that a much more accurate prognosis can be given from clinical data than from laboratory data.

The formula is recommended as being most valuable because (*a*) it is simplest, (*b*) it indicates percentage mortality directly without referring to a table or graph, (*c*) it is more accurate than either severity index and (*d*) it permits estimation of the severity of diabetic coma by simple examination without waiting for reports of chemical study of the blood.

SUMMARY AND CONCLUSIONS

A study of the various factors influencing the mortality in 315 cases of diabetic coma at the Los Angeles County General Hospital brings out the following:

1. Mortality statistics in diabetic coma are of no value unless attacks of coma of equal severity are compared.

2. Coma occurs more frequently during the puberal and the climacteric decade. Mortality is equal in the two sexes.

3. In the great majority of cases death in diabetic coma is due to shock or associated complicating disease. One half of all fatalities in coma occur between six and twenty-four hours after admission to the hospital.

4. Factors of greatest importance and of fundamental nature influencing the mortality of diabetic coma are (*a*) the age of the patient, (*b*) the diastolic blood pressure, (*c*) the degree of unconsciousness and (*d*) complicating diseases.

8. Dillon and Dyer.[1c] Wilder.[5a]

5. Factors of lesser importance in estimating severity of diabetic coma are (*a*) duration of coma, (*b*) blood nonprotein nitrogen and (*c*) blood sugar.

6. There is no relation between the carbon dioxide–combining power of the blood and mortality.

7. A modified index of severity is recommended for use in estimating severity of diabetic coma.

8. A severity formula is also derived which indicates severity of coma and allows one to predict average prospective mortality.

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INTERRELATION OF THE FACTORS INFLUENCING MORTALITY IN DIABETIC COMA

A STATISTICAL STUDY

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A study [1] of the various factors influencing the mortality of diabetic coma in 315 consecutive cases at the Los Angeles County General Hospital from 1930 through 1940 brought out the following conclusions:

1. Factors of greatest importance in influencing the mortality of diabetic coma are (*a*) the age of the patient, (*b*) the level of diastolic blood pressure, (*c*) the degree of unconsciousness of the patient and (*d*) the severity of the complicating disease.

2. Factors of lesser importance in estimating severity of diabetic coma are (*a*) the duration of coma before treatment is instituted, (*b*) the level of blood nonprotein nitrogen and (*c*) the level of blood sugar.

3. There is no relation between the carbon dioxide–combining power of the blood and mortality.

The previous study suggested that perhaps some of these factors are "primary," whereas others are "secondary," produced by and dependent on fundamental changes in the primary factors. For example, may it be assumed that elevation of blood nonprotein nitrogen is a secondary factor depending on age and blood pressure? Does severity of shock, acidosis, hyperglycemia or azotemia increase the longer the patient is in coma? Is the height of blood sugar dependent on the value of the carbon dioxide–combining power of the blood or vice versa? In an attempt to answer these and other similar questions cross analysis of the various factors was undertaken.

Theoretically, in a study of the relation of two interdependent variables, all other factors should be kept constant. For example, to study the relation of blood nonprotein nitrogen to age, a group of cases of uncomplicated coma should be selected in which there are the same degree of unconsciousness, height of blood pressure, level of blood sugar and carbon dioxide–combining power, etc., so that the only known

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Dr. Solomon Strouse contributed assistance, criticism and suggestions during the preparation of this paper.

1. Collen, M. F.: Mortality in Diabetic Coma, Arch. Int. Med., this issue, p. 347.

variables would be age and nonprotein nitrogen. This was attempted, and it was soon discovered that too few cases fell into each restricted group to warrant any deduction. Therefore, two variables were plotted against one another, on the assumption that the other factors would tend to balance out.

METHOD OF ANALYSIS

Figure 1 exemplifies the method used to study the interrelation of two factors. In this graph the cross analysis of the relation between blood sugar and the carbon dioxide–combining power of the blood is attempted. It is noted that of

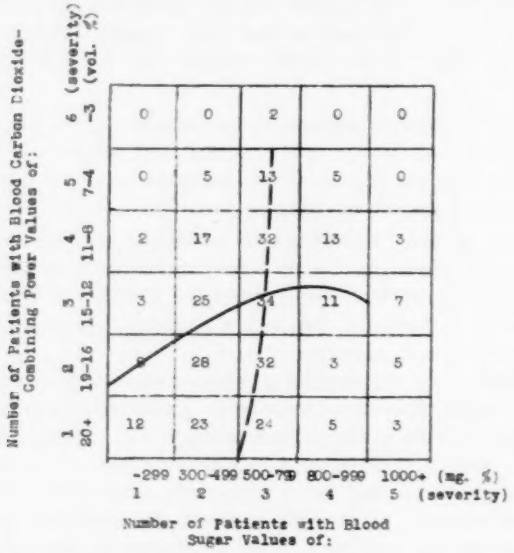
Number of Patients with Blood Carbon Dioxide-Combining Power Values of:
6 (severity) (vol. %)
1 20+ 0 0 2 0 0
2 19-16 0 5 13 5 0
3 15-12 2 17 32 13 3
4 11-8 3 25 34 11 7
5 7-4 6 28 32 3 5
6 -3 12 23 24 5 3
-299 300-499 500-799 800-999 1000+ (mg. %)
1 2 3 4 5 (severity)
Number of Patients with Blood Sugar Values of:

Fig. 1.—Interrelation of blood sugar and the carbon dioxide–combining power of the blood.

25 patients with blood sugar values of 299 mg. per hundred cubic centimeters or lower (severity of grade 1), 12 patients had a carbon dioxide–combining power of 20 volumes per cent or over (severity of grade 1), 8 had values of 19 to 16 volumes per cent (severity of grade 2), 3 had values of 15 to 12 volumes per cent (severity of grade 3) and 2 had values of 11 to 8 volumes per cent (severity of grade 4), with an average carbon dioxide–combining power for the whole group of about 19 volumes per cent. Similarly, patients with blood sugar values from 300 up to and including 499 mg. per hundred cubic centimeters (severity of grade 2) had carbon dioxide–combining power graded as follows: severity of grade 1, 23 patients; grade 2, 28 patients; grade 3, 25 patients; grade 4, 17 patients, and grade 5, 5 patients, with an average carbon dioxide–combining power for the group of about 16 volumes per cent. In like manner, it is determined that patients with blood sugar values from 500 to 799 mg. per hundred cubic centimeters (severity of grade 3) had an average carbon dioxide–

combining power of about 5 volumes per cent, patients with blood sugar values of 800 to 999 mg. per hundred cubic centimeters (severity of grade 4) had an average carbon dioxide-combining power of 12 volumes per cent and patients with blood sugar values of 1,000 mg. per hundred cubic centimeters or over (severity of grade 5) had an average carbon dioxide-combining power of about 15 volumes per cent. These average carbon dioxide-combining powers lie along the heavy solid line (fig. 1), which therefore indicates the relation between carbon dioxide-combining power of the blood and blood sugar, with blood sugar used as the independent factor and carbon dioxide-combining power as the dependent factor. In other words, it indicates whether and how carbon dioxide-combining power varies with blood sugar. It is evident that carbon dioxide-combining power definitely falls as blood sugar rises.

By using the same figure 1 and laying it on its side, the study may be repeated, with the carbon dioxide-combining power of the blood as the independent factor and blood sugar as the dependent factor. It is seen that of patients with a carbon dioxide-combining power of 20 volumes per cent or over (severity of grade 1), 12 patients had blood sugar values of 299 mg. per hundred cubic centimeters or under, 23 patients had values from 300 to 499 mg., 24 patients had values from 500 to 799 mg., 5 patients had values of 800 to 999 mg. and 3 patients had values of 1,000 mg. or over, with an average blood sugar value for the group of about 450 mg. per hundred cubic centimeters. Likewise, for each severity grade of carbon dioxide-combining power, the average blood sugar value is determined, and a second curve is obtained (fig. 1), indicated by the vertical broken line, which shows the variation of blood sugar with the carbon dioxide-combining power of the blood. It is evident that as the carbon dioxide-combining power falls, sugar on the average slightly rises.

It must be appreciated that the two curves obtained from the graph were calculated from the use of two separate sets of figures, even though these figures were all included within the same graph; the curve showing the dependency of the carbon dioxide-combining power of the blood on blood sugar was obtained by taking averages in a vertical direction, whereas the second curve, showing the dependency of blood sugar on carbon dioxide-combining power, was taken by averaging a different set of numbers in a horizontal direction.

In a similar manner through the use of thirty-two comparable graphs (too extensive to reproduce here), sixty-four curves were obtained, showing the interrelation of eight variables. These curves are aggregated and plotted to scale on one graph (fig. 2) for convenience and comparison.

Figure 2 shows the interrelation, through cross analysis, of the various factors influencing the severity and mortality of diabetic coma. Each factor is analyzed as though it were an independent fundamental factor, with all the other factors secondary. The factors are plotted according to their severity; namely, 0, normal level or absence of the factor; 1, the mildest degree, and 5, the most severe degree.

RESULTS

Age.—In studying the dependency of the factors on the age of the patients, figure 2*a* has the abscissa (base line) divided into five groups, group 1 (15 years and under), group 2 (16 to 30 years), group 3 (31 to 50 years), group 4 (51 to 70 years) and group 5 (71 years and over). The following observations may be noted:

1. Average blood pressures, systolic and diastolic, in all age groups are about the same; patients in the older age groups do not tend to go

into shock more easily than children. However, in this series of cases it was rare for a patient over 45 years of age to go into shock and recover, whereas younger persons were admitted completely unconscious with blood pressures of zero and recovered.

2. The duration of coma is equal in all age groups. Children are not brought into the hospital earlier than adults.

3. The average values for blood sugar and blood nonprotein nitrogen are somewhat higher in the older age groups. These may be minor contributing factors to the higher mortality of aged patients, since it has been shown [1] that mortality is directly proportional to blood nonprotein nitrogen and somewhat dependent on blood sugar.

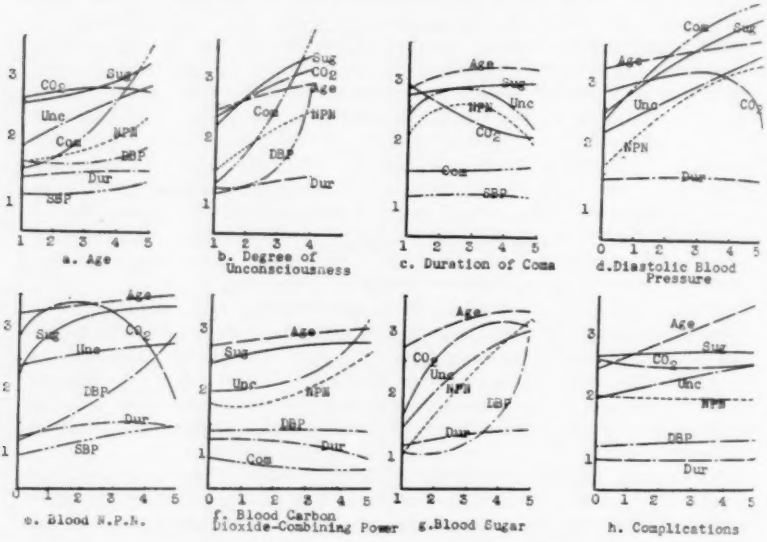

Fig. 2.—Interrelation of various factors influencing the severity of diabetic coma. The following abbreviations have been employed: *Sug*, blood sugar; *CO_2*, carbon dioxide–combining power of the blood; *NPN*, nonprotein nitrogen content of the blood; *Unc*, degree of unconsciousness; *Com*, severity of complications; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure, and *Dur*, duration of coma.

4. The carbon dioxide–combining power of the blood has no relation to age. Aged patients do not go into acidosis more easily than children, or vice versa.

5. Patients in the older age groups have, on the average, a more severe degree of unconsciousness on admission. This may indicate that in "coma" they become unconscious more easily than do children, and may also be a contributing factor toward the increased mortality of the aged patients.

6. It is at once evident that the severity of complications is probably the most important single factor explaining the increased mortality of the older age groups. Figure 2*a* shows that complications in patients below 50 years of age are of mild severity. Complications are moderately frequent in children, being mostly acute infections of the upper respiratory tract with or without complicating otitis media, etc., with low mortality. In the older age group the majority of comas in this series of cases were complicated, and the majority of complications were pneumonia, heart disease and gangrene of the feet with sepsis, all severe complications usually warranting a severity grade of 4 or 5. Complications are not only more severe in older age groups but are more frequent. In this series, of those cases in which the patients were under 15 years of age, 40 per cent of the comas were complicated; of patients from 31 to 50 years, 53 per cent had complications, and of those patients over 70 years of age, 71.5 per cent had complications.

In summary, the age of the patient influences many factors; as age increases, severity and frequency of complications markedly increase, degree of unconsciousness definitely increases and average values for blood sugar and blood nonprotein nitrogen increase.

Degree of Unconsciousness.—Figure 2*b* shows the dependency of the various factors on the degree of unconsciousness. The base line is calibrated as 1 (drowsy), 2 (semiconscious), 3 (unconscious but responding to painful stimuli) and 4 (completely unconscious). Studying these curves, one finds the following statements can be made:

1. Although figure 2*a* shows that the degree of unconsciousness is dependent on age, the converse is not as marked. In other words, although elderly patients tend to have, on the average, a more marked degree of unconsciousness, unconscious patients are found to have an average age only moderately higher than that of drowsy patients. A 60 year old patient in coma has a 50 per cent chance of being unconscious (group 3) and only a 20 per cent chance of being drowsy. A patient admitted unconscious in diabetic coma has a 35 per cent chance of being 60 years old and a 20 per cent chance of being 25 years of age.

2. Duration of coma is practically independent of degree of unconsciousness. Unconscious patients on the average have been in coma only slightly longer than drowsy patients.

3. Blood pressure definitely varies with the degree of unconsciousness. As the degree of unconsciousness becomes more severe, the diastolic blood pressure rapidly falls. The majority of completely unconscious patients are in severe shock.

4. Rising values for blood sugar and blood nonprotein nitrogen and a falling value for the carbon dioxide–combining power of the blood all increase in severity with increasing depth of unconsciousness. Blood sugar and blood nonprotein nitrogen increase definitely, completely

unconscious patients having on the average one severity grade higher than drowsy patients. Although the severity of acidosis increases with the degree of unconsciousness, the changes are not as striking. The degree of acidosis increases (the carbon dioxide–combining power of the blood falls) only one-half a severity degree from drowsiness to complete unconsciousness.

5. Again, it is noted that the severity of complications is the most important factor of all. Patients admitted unconscious or completely unconscious usually have complications, the complicating disease usually being severe. In this series, if one considers only cases of complication in which the patient was unconscious (grade 3), the average severity of the complication was grade 4. It becomes apparent that the degree of unconsciousness of the patient influences all factors. It is a good indication of the severity of the complication and the degree of shock and is closely linked with age and with chemical changes in the blood.

Duration of Coma.—Figure *2c* indicates the influence of the duration of coma on the various factors. The duration of coma is divided into five groups, 1 (twelve hours and under), 2 (thirteen to twenty-four hours), 3 (twenty-five to thirty-six hours), 4 (thirty-seven to forty-eight hours) and 5 (forty-nine hours and over).

1. It is interesting to note that the carbon dioxide–combining power of the blood definitely rises with duration of coma. It has also been demonstrated [1] that as duration of coma increases, mortality first rises, then falls; as the value of carbon dioxide–combining power falls, mortality first tends to fall, then later rises. Figure *2f* also indicates the inverse relation between carbon dioxide–combining power and duration of coma; the lower values of carbon dioxide–combining power are usually associated with comas of short duration; the higher values of carbon dioxide–combining power, on the average, are present in patients who have been in coma over a longer period.

2. As duration of coma increases, the average degree of unconsciousness and the level of blood nonprotein nitrogen rise, to reach a peak at about thirty-six hours; then the severity of these factors decreases as time goes on.

The graphs indicate that after a patient has been in coma thirty-six to forty-eight hours, the average degree of unconsciousness, the level of blood nonprotein nitrogen and the percentage of mortality fall. It is suggested that untreated patients in coma and still alive after forty-eight hours survive because they can better tolerate acidosis.

Blood Pressure.—Figure *2d* indicates the important influence of diastolic blood pressure on the various factors. Diastolic blood pressure is plotted along the abscissa in six groups, group 0 (over 70 mm. mercury), group 1 (69 to 60 mm. mercury), group 2 (59 to 50 mm. mercury), group 3 (49 to 40 mm. mercury), group 4 (39 to 30 mm. mercury) and group 5 (29 mm. mercury and under).

1. It is evident that all the important factors, namely, degree of unconsciousness, severity of complications, blood sugar and blood nonprotein nitrogen, rapidly increase in severity as blood pressure falls and depth of shock increases. This merely stresses the importance of blood pressure as a fundamental factor influencing the severity of coma.

2. Average age and duration of coma are not influenced by blood pressure to any significant degree. Shock is not more frequently present in aged patients than in young ones.

3. Peculiarly enough, the value of the carbon dioxide–combining power of the blood is usually relatively high in the most severe cases of shock; the lowest blood pressures tend to be accompanied by the highest values for carbon dioxide–combining power. It is shown in figure *2f* that blood pressure is not dependent on the carbon dioxide–combining power.

Blood Nonprotein Nitrogen.—In figure *2e* blood nonprotein nitrogen is plotted along the abscissa in six groups, group 0 (values below 40 mg. per hundred cubic centimeters), group 1 (41 to 60 mg.), group 2 (61 to 80 mg.), group 3 (81 to 100 mg.), group 4 (101 to 120 mg.) and group 5 (121 mg. and over).

1. Outstanding in figure *2e* is the finding that diastolic blood pressure is definitely influenced by the degree of azotemia and that systolic blood pressure is affected to a lesser degree. Comparing figures *2d* and *e*, one sees that blood nonprotein nitrogen varies with the diastolic blood pressure, just about the same as blood pressure varies with blood nonprotein nitrogen; there is a direct linear relation between the two.

2. Blood sugar increases with rising blood nonprotein nitrogen in the lower degrees of azotemia. After blood nonprotein nitrogen reaches about 80 mg. per hundred cubic centimeters, there is no further rise in average blood sugar values.

3. The carbon dioxide–combining power of the blood shows a remarkable relation to blood nonprotein nitrogen. The average level of carbon dioxide–combining power falls in lower degrees of azotemia, but in those cases in which uremia is definitely marked the carbon dioxide–combining power of the blood tends to be relatively high. Of 8 patients with values for blood nonprotein nitrogen over 100 mg. per hundred cubic centimeters, 3 patients had values for carbon dioxide–combining power of over 20 volumes per cent; the lowest value for this factor in this group was 8.9 per cent.

4. The degree of unconsciousness, age and duration of coma are not remarkably influenced by blood nonprotein nitrogen.

5. If one considers all cases, high values for blood nonprotein nitrogen are found just as frequently in uncomplicated, as in complicated, comas (not graphed). With the exception of uremia due to

primary nephritis with associated diabetic coma, there is no relation between average levels of blood nonprotein nitrogen and severity of complications.

Carbon Dioxide–Combining Power of the Blood.—Figure *2f* indicates the influence of the carbon dioxide–combining power of the blood on the various factors. The carbon dioxide–combining power is plotted along the abscissa in six groups, group 0 (20 volumes per cent or over), group 1 (19 to 16 volumes per cent), group 2 (15 to 12 volumes per cent), group 3 (11 to 8 volumes per cent), group 4 (7 to 4 volumes per cent) and group 5 (3 volumes per cent or lower).

1. As the carbon dioxide–combining power of the blood falls, the degree of unconsciousness increases.

2. The blood nonprotein nitrogen rises moderately as the carbon dioxide–combining power falls. Since it has been demonstrated that diabetic acidosis produces renal tubular damage,[2] the deduction that increasing severity of acidosis would produce increasing azotemia is supported.

3. As discussed with reference to figure *2c*, an inverse relation appears to exist between duration of coma and level of carbon dioxide–combining power. Figure *2f* indicates that the lower values for carbon dioxide–combining power tend to be associated with comas of shorter duration.

4. Blood sugar is influenced only slightly by the carbon dioxide–combining power; a low value for the latter factor tends to be associated with slightly higher blood sugar levels than does a high value.

5. Age, blood pressure and severity of complications are not influenced to any remarkable degree by the level of the carbon dioxide–combining power. On the whole, figure *2f* is notable by the absence of any influence of the carbon dioxide–combining power on the majority of severity factors, which again tends to minimize the importance of this factor in evaluating the severity of a diabetic coma.[3]

Blood Sugar.—Figure *2g* shows the influence of blood sugar on the various factors. Blood sugar is plotted along the abscissa in five groups, group 1 (299 mg. per hundred cubic centimeters and under), group 2 (300 to 499 mg.), group 3 (500 to 799 mg.), group 4 (800 to 999 mg.) and group 5 (1,000 mg. and over).

The following observations may be made:

1. Blood nonprotein nitrogen definitely increases with rising blood sugar. Figures *2e* and *g* reveal that a close relation exists

2. Tollman, J. P., and Kirk, E. J.: Diabetes Mellitus with Reference to Kidney Pathology, Am. J. Clin. Path. **6**:357-370, 1936.

3. Rabinowitch, J. M.; Fowler, A. F., and Bensley, E. H.: Diabetic Coma, Ann. Int. Med. **12**:1403-1428, 1939. Collen.[1]

between the two factors, a rise in one tending to be associated with a rise in the other; however, statistically, blood nonprotein nitrogen appears to be more dependent on blood sugar than vice versa.

2. The degree of unconsciousness varies with the level of blood sugar. With blood sugar values over 800 mg. per hundred cubic centimeters patients are usually unconscious, while with values under 500 mg. patients are usually semiconscious to drowsy.

3. Diastolic blood pressure definitely varies with blood sugar values, especially in cases of marked hyperglycemia. As blood sugar levels rise over 800 mg. per hundred cubic centimeters, blood pressure rapidly falls.

4. Average age, duration of coma and severity of complications (not shown on the graph) show slight increase with rising blood sugar levels.

5. Blood sugar is an important factor definitely influencing many of the variables which determine the severity of diabetic coma.

Complicating Diseases.—In figure 2*h* an attempt is made to study the influence of the presence of complications on the various factors. The complications are graded according to estimated severity from 1 (very mild) to 5 (very severe) and are plotted along the abscissa. The first group (0) comprises cases in which complications are not present.

1. Again the relation between age and complicating conditions is outstanding. It is evident that the more severe grades of complicating diseases are present in the older age groups.

2. It is also noted that the degree of unconsciousness rises with increasing severity of complication; however, this is not pronounced.

3. Blood sugar, blood nonprotein nitrogen and the carbon dioxide–combining power of the blood are not influenced by complicating diseases, indicating that the primary metabolic disturbances of diabetic coma are not essentially altered by a complication.

4. Blood pressure and duration of coma are not influenced by absence or presence of complications.

SUMMARY OF CROSS ANALYSIS OF FACTORS

A study of 315 cases of diabetic coma at the Los Angeles County General Hospital has brought out several factors which influence the mortality of diabetic coma. Cross analysis of the interrelation of these factors reveals:

1. The increasing mortality with age is primarily due to the increased number and the increased severity of complications in older age groups.

2. The degree of unconsciousness of a patient in diabetic coma varies with blood pressure, blood sugar, the carbon dioxide–combining

power of the blood, age and severity of the complicating disease in decreasing importance. The high mortality in severe degrees of unconsciousness is predominantly due to the presence of increased frequency and severity of complications and severe shock.

3. Duration of coma is of secondary importance; however, patients in diabetic coma who are untreated for over forty-eight hours and who are still alive form an interesting small group who seem to tolerate acidosis well and have only moderately severe coma.

4. The degree of shock varies with the degree of unconsciousness and the values for blood nonprotein nitrogen and blood sugar.

5. The degree of azotemia primarily varies with the blood sugar and the blood pressure and to a lesser extent with the degree of unconsciousness, age and the carbon dioxide–combining power of the blood in the order named. The high mortality in severe azotemia is probably due to associated shock, there being a direct relation between diastolic blood pressure and blood nonprotein nitrogen.

6. The carbon dioxide–combining power of the blood decreases with rising blood sugar and increasing depth of unconsciousness.

7. The degree of hyperglycemia is influenced by diastolic blood pressure and to a lesser extent by the degree of unconsciousness.

8. Although the presence of a complicating disease is an important factor influencing the mortality of a patient in coma, it does not appear to influence the level of blood sugar or blood nonprotein nitrogen or the carbon dioxide–combining power of the blood.

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EXPERIMENTAL PRODUCTION OF EMPHYSEMA

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Emphysema is encountered in 2 to 5 per cent of all necropsies.[1] If we exclude the senile type of emphysema and those rare instances of emphysema due primarily to disease of the thorax, it may be said that it is a condition associated with bronchitis and bronchial spasm. These disorders obstruct respiration and bring about persistent pulmonary overdistention. Coughing, which always accompanies them, is thought to exaggerate this distention. Attacks of asthma are nearly always associated with pulmonary emphysema, and hay fever is becoming more important in any study of the disease.

Important in the emphysematous lung is the destruction of many capillaries in thin, atrophic alveolar walls, resulting in an obstructed pulmonary circulation.[2] This may lead to a high pulmonary arterial pressure with hypertrophy of the right side of the heart. Statistics compiled from autopsy material by various authors are not in agreement as to the incidence of this cardiac hypertrophy, but it is present in a varying percentage of cases.[3] The peripheral venous pressure is increased.[4] Vital capacity is reduced.[5] This is marked in cases of

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From the Department of Surgery, University of Chicago.

This work was done under a grant of the Douglas Smith Foundation, of the University of Chicago.

1. Christie, R. V.: Emphysema of the Lung, in Rolleston, H.: The British Encyclopaedia of Medical Practice, London, Butterworth & Co., Ltd., 1937, vol. 4, pp. 508-519.

2. Hamman, L.: Emphysema, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1940, vol. 2, pt. 1, pp. 68-81.

3. Alexander, H. L.; Luten, D., and Kountz, W. B.: The Effects on the Heart of Long-Standing Bronchial Asthma, J. A. M. A. **88**:882-884 (March 19) 1927. Kahn, M. H.: The Electrocardiogram in Bronchial Asthma, Am. J. M. Sc. **173**:555-562, 1927. Unger, L.: Heart in Bronchial Asthma, J. Allergy **2**:17-22, 1930. MacDonald, I. G.: The Local and Constitutional Pathology of Bronchial Asthma, Ann. Int. Med. **6**:253-277, 1932. Huber, H. L., and Koessler, K. K.: The Pathology of Bronchial Asthma, Arch. Int. Med. **30**:687-760 (Dec.) 1922. Criep, L. H.: Bronchial Asthma and Circulation, ibid. **49**:241-252 (Feb.) 1932.

4. Kountz, W. B.; Alexander, H. L., and Dowell, D.: Emphysema Simulating Cardiac Decompensation, J. A. M. A. **93**:1369-1371 (Nov. 2) 1929.

(Footnotes continued on next page)

severe emphysema, and there is an inability to cope with increased metabolic activities.

Efforts at active treatment of emphysema have been discouraging to say the least. Perhaps preventive therapeusis has more to offer. Thus more effort should be made to eliminate the cause, if that is possible.

THEORIES OF PATHOGENESIS

Several important types of emphysema have been recognized, namely, hypertrophic, or chronic obstructive, emphysema; atrophic, or senile, emphysema; acute vesicular emphysema associated with acute infections of the respiratory tract; localized, or compensatory, emphysema due to atelectasis or fibrosis, and surgical emphysema, or acute interstitial emphysema, associated with chest injuries or artificial pneumothorax.[1] Of this group probably the most important is hypertrophic, or chronic obstructive, emphysema.

Important factors to be considered in the production of emphysema are (1) increased pressure in the alveoli and (2) the resistance of the alveolar wall.[2] Of these, distention of the alveoli by increased pressure is usually thought to be the more important, especially in the obstructive type. Increased expiratory pressure with hyperpnea when inspiration is unobstructed leads to pulmonary distention. There is also a reflex increase in the force of inspiration. Coughing leads to an enormous increase in the expiratory pressure. It is the effects of combined inspiratory and expiratory pressures in the alveoli which cause the greatest degree of pulmonary distention and which if long maintained are believed to lead to true substantive emphysema. Emphysema is commonly encountered as a result of chronic bronchitis and asthma. In cases of chronic bronchitis the degree of obstruction to all parts of the lung varies because of edema, infection and the presence of tenacious secretions. The parts supplied by the most obstructed bronchi become distended, even though there is no hyperpnea. Normally the force of inspiration is greater than that of expiration. The elasticity of the lung and thorax is sufficient to deflate the unobstructed lung but not to deflate fully the obstructed parts. Increase in respiratory effort leads only to increased pulmonary distention. This eventually may lead to permanent dilatation of the alveoli.

Changes in the Thorax.—Freund[6] first described degenerative changes which lead to an increase in the size of the thorax. He men-

5. (*a*) Kountz, W. B., and Alexander, H. L.: Emphysema, Medicine **13**:251-316, 1934. (*b*) Macklin, C. C.: Transport of Air Along Sheaths of Pulmonic Blood Vessels from Alveoli to Mediastinum, Arch. Int. Med. **64**:913-926 (Nov.) 1939. (*c*) Hamman.[2]

6. Freund, W. A.: Der Einfluss der primären Erkrankungen des knorpligen Thorax auf Entstehung gewisser Lungenkrankheiten, Verhandl. d. phys.-med. Gesellsch. in Würzburg **9**:223, 1859.

tioned the lengthening and thickening of the costal cartilages and the ribs. Other authors expressed the belief that kyphosis of the thoracic portion of the spine was important in altering the size of the chest and as a cause of emphysema.[7] The atrophic changes of old age may be a factor in the production of emphysema. There is a tendency for the chest to become barrel-shaped, thus increasing the thoracic space and leading to so-called "senile emphysema."

Heredity.—Some authors have proposed that there is an inherited tendency to such conditions as chronic bronchitis and asthma which lead to emphysema. Further, they have suggested that developmental defects of the bony thorax may lead to emphysematous changes in the lungs.[8]

Defects in the Lung and the Pleura.—Such degenerative and developmental changes are more apt to be secondary than primary in the causation of emphysema.

Occupational Factors.—In glass blowing and wind instrument playing there is increased expiratory pressure. This leads to pulmonary distention which may become permanent, but not to emphysema. It would seem that emphysema does not develop in the absence of hyperpnea.[9]

PREVIOUS ATTEMPTS AT EXPERIMENTAL PRODUCTION OF EMPHYSEMA

According to Harris and Chillingworth,[10] the first attempts to produce emphysema were made by use of a plethysmograph which enclosed an animal's entire body in a negative pressure chamber. The trachea was connected with the outside atmospheric pressure, so that the intrapulmonary pressure was in excess of the extrathoracic pressure of the chamber. This method did not simulate natural conditions of the disease, so these workers devised a ball valve type of obstruction which was placed in the trachea of dogs. They made studies which varied from twenty-four hours to three weeks in duration. Pathologic changes characteristic of emphysema except for the production of fibrous tissue developed in their dogs. Prolonged, or chronic, experiments were not done, nor was the intrapulmonary pressure measured.

7. Loeschcke, H.: Aus Lungenemphysem, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 3, pt. 1, pp. 612-700.

8. Engelhard, A.: Lungenemphysem aus bronchialer Lungenbläkung, Deutsches Arch. f. klin. Med. **175**:38-49, 1933.

9. Kaltreider, N. L.: Pathological Physiology of Emphysema, Internat. Clin. **2**:83-111, 1936. Kountz and Alexander.[5a]

10. Harris, W. H., and Chillingworth, F. P.: The Experimental Production in Dogs of Emphysema with Associated Asthmatic Syndrome by Means of an Intratrachreal Ball Valve, J. Exper. Med. **30**:75-85, 1919.

Friedman and Jackson [11] made studies of the carbon dioxide content of the blood and the alveolar air during obstructed expiration, such as occurs in asthma, and concluded that the increased intrabronchial pressure interferes with the free flow of blood through the pulmonary capillaries, resulting in venous stasis and accumulation of carbon dioxide in the blood. This, in turn, causes an increase in the carbon dioxide of the alveolar air. They produced emphysematous changes in animals by the use of a valve which was placed in the trachea. That is, the alveoli were dilated and ruptured, but production of fibrous tissue was not noted. Their experiments were of the acute type, lasting three to eight hours. The pressure in the carotid artery was also studied and observed to drop consistently even with a slight increase in the intrabronchial pressure.

Kountz, Alexander and Dowell [4] reported a large series of cases of advanced emphysema with its associated effect on the heart. Experimental studies on dogs, in which a ball valve had been used, showed that extensive emphysema could be produced in a few weeks. They concluded that advanced emphysema does not necessarily affect the heart and that peripheral venous pressure varies directly with changes in pressure in the pleural cavity.

Kountz, Pearson and Koenig [12] attempted to determine the point of obstruction to the venous return in instances of emphysema with increased intrapleural pressure. They concluded that although there may have been some obstruction to the normal blood flow through the lungs, the chief obstruction was at or peripheral to the entrance of blood into the thorax. Certainly the delay occurred before the blood reached the right side of the heart.

Hinshaw [13] made further attempts at production of emphysema by a modification of the original ball valve type of tracheal obstruction.

Paine,[14] studying the changes in elasticity and histologic structure of the lung, inserted special valves into the trachea in dogs to produce respiratory obstruction and used operative procedures tending to change the thorax in dogs. He concluded that emphysematous changes of the pulmonary parenchyma occur within four to thirty-four weeks when either inspiration or expiration is obstructed and that similar changes

11. Friedman, E. D., and Jackson, H. C.: The Carbon Dioxide Content of Blood and of Alveolar Air in Obstructed Expiration, Arch. Int. Med. **19**:767-776 (May) 1917.

12. Kountz, W. B.; Pearson, E. F., and Koenig, K. F.: Observations on Intrapleural Pressure and Its Influence on Relative Circulation Rate in Emphysema, J. Clin. Investigation **11**:1281-1291, 1932.

13. Hinshaw, H. C.: Experimental Production of Chronic Obstructive Emphysema in Animals, Proc. Staff Meet., Mayo Clin. **13**:599-600, 1938.

14. Paine, J. R.: Experimental Production of Pulmonary Emphysema, J. Thoracic Surg. **10**:151-175, 1940.

occur within eighteen to twenty-five weeks if the anterior portion of the diaphragm is reefed.

In most of these experiments prolonged studies were not attempted.

Previous work on the effects of known positive pressure in intratracheal anesthesia was done in this department by Marcotte and associates.[15] Their work indicated certain dangers in increased intrabronchial pressure. They found that mediastinal emphysema, pneumothorax and laceration of the pulmonary tissues were produced by pressures as low as 18 mm. of mercury. The mechanism of this phenomenon has been well explained by Macklin.[16] Moreover, once mediastinal emphysema had occurred, it tended to continue, even though the pressure dropped below the level necessary to initiate it. It was also noted that intrabronchial pressure depends chiefly on the patency of the outlet rather than the pressure at which air is forced into the lungs.

EXPERIMENTAL PROCEDURE

In our present work we have attempted to carry out acute and chronic experiments testing the theory of the production of emphysema by elevated intrabronchial pressure. An attempt was made to simulate in dogs the short inspiration and the prolonged difficult expiration of a person with chronic asthma at the height of an attack. In a person with asthma expiration is accompanied by a relatively marked increase in intrabronchial pressure because of the obstructed air passages; whereas inspiration is not accompanied by any increase in intrabronchial pressure.

Intermittent overinflation of the lungs was carried out in biweekly fifteen minute periods with controlled intrabronchial pressure. Air was introduced under positive pressure into the trachea near the primary bifurcation (carina) and permitted to escape back through the upper part of the trachea and the mouth. This outlet was obstructed so that various pressures could be maintained within the bronchial tree. The period during which air was introduced was arbitrarily three times as long as the period during which the air escaped, in keeping with the longer expiratory period of an asthmatic person. This intermittent overinflation was carried out at a rate of approximately twenty-eight times per minute, or about the normal respiratory rate in dogs. Experiments with 2 dogs were carried on for eleven months.

Ten dogs were used (table 1). Three were used for acute study and 7 for chronic study. On 3 of the latter group acute studies were also made at the end of the period of chronic study. The acute experiments varied from thirty-five to seventy-seven minutes in duration; the chronic, from one week to eleven months. The number of inflations with intermittent positive pressure varied from one to seventy-six, and the intrabronchial pressures, from 20 to 50 mm. of mercury, 35 mm. of mercury being the usual pressure in the chronic experiments.

Apparatus.—This consisted of a modified windshield wiper which was attached to an air source. The wiper was so constructed that the pressure delivered and the length of the "on" cycle and rate per minute could be easily adjusted. Large

15. Marcotte, R. J.; Adams, W. E.; Phillips, F. J., and Livingstone, H.: Differential Intrabronchial Pressures and Mediastinal Emphysema, J. Thoracic Surg. **9**:346-355, 1940.

16. Macklin, C. C.: Pneumothorax with Massive Collapse from Experimental Local Over-Inflation of Lung Substance, Canad. M. A. J. **36**:414-420, 1937.

Summary of Results of Overinflation of Lungs of Ten Dogs with Intermittent Positive Pressure

	Dog No.	Type of Experiment	Duration of Experiment	No. of Experiments	Intrabronchial Pressure, Mm. Hg	Physiologic Effects: Average Blood Pressure, Mm. Hg			Physiologic Effects: Average Pulse Rate, Beats per Min.			Cause of Death	Pathologic Condition: Gross Examination	Pathologic Condition: Microscopic Examination
						Initial	Inflation: During	Inflation: After	Initial	Inflation: During	Inflation: After			
1	884	Acute	77 min.	1	22	170	110	...	...	...	...	Acute experiment with pressure studies	Mediastinal emphysema; heart and lungs grossly normal	
2	157	Acute	47 min.	1	20	90	70	...	...	...	...	Acute experiment with pressure studies	Moderate mediastinal emphysema; heart and lungs grossly normal	Interstitial emphysema; slight dilatation of terminal respiratory units
3	182	Acute	42 min.	1	50	160	80	...	...	...	...	Acute experiment with pressure studies; probable failure of right side of heart	No mediastinal emphysema; heart and lungs apparently normal	Interstitial emphysema; slight dilatation of terminal respiratory units; also thickening of pleura with pigment-containing macrophages present subpleurally
4	682	Chronic	1 wk.	2	35	...	...	...	...	...	...	Mediastinal emphysema; air embolism	Mediastinal emphysema; air embolism; pulmonary hemorrhage	Interstitial emphysema; some dilatation of terminal respiratory units
5	683	Chronic	1 wk.	2	35	...	...	...	...	...	...	Mediastinal emphysema; air embolism	Mediastinal emphysema; air embolism; pulmonary hemorrhage	Interstitial emphysema; some dilatation of terminal respiratory units
6	711	Chronic	2½ wk.	4	35	146	...	104	163	155	151	Mediastinal emphysema; spontaneous pneumothorax	Spontaneous pneumothorax; mediastinal emphysema; air embolism; pulmonary hemorrhage	Interstitial emphysema; some dilatation of terminal respiratory units
7	496	Chronic	7 mo.	39	35	124	85	144	149	137	142	Mediastinal emphysema; spontaneous pneumothorax	Pneumothorax; mild mediastinal emphysema	Slight interstitial emphysema; dilatation of terminal respiratory units; unresolved pneumonia with pulmonary emphysema; respiratory pores enlarged and irregular
8	754	Chronic	7½ mo.	49	35	139	108	158	159	185	145	Acute experiment with pressure studies	See 11 below	
9	657	Chronic	8 mo.	47	35	124	96	141	184	199	174	Acute experiment with pressure studies	See 12 below	
10	341	Chronic	11 mo.	75	35	128	123	147	178	196	178	Acute experiment with pressure studies	See 13 below	Middle lobe of right lung removed after 2 mo.; some dilatation of terminal respiratory units; respiratory pores enlarged and irregular
11	754	Chronic and acute	48 min.	50	35	170	128	...	...	...	...	Acute experiment with pressure studies	No mediastinal emphysema; heart and lungs apparently normal	Less interstitial emphysema than in dogs 157 and 182; dilatation of terminal respiratory units with slight fragmentation of alveolar walls; respiratory pores enlarged and irregular
12	657	Chronic and acute	40 min.	48	35	120	70	...	...	...	...	Acute experiment with pressure studies	No mediastinal emphysema; heart and lungs apparently normal	Less interstitial emphysema than in dogs 157 and 182; dilatation of terminal respiratory units with slight fragmentation of alveolar walls; respiratory pores enlarged and irregular
13	341	Chronic and acute	35 min.	76	26	150	122	...	...	...	...	Acute experiment with pressure studies	No mediastinal emphysema; heart and lungs apparently normal	Less interstitial emphysema than in dogs 157 and 182; dilatation of terminal respiratory units with slight fragmentation of

rubber tubing led from the wiper to the trachea. Within this tube was a smaller tube leading from a mercury manometer to the exit of air within the bronchial tree. This double tubing was led through a tight face mask and airway down to the carina. The mask had an adjustable air outlet for regulation of intratracheal pressure and escape of air (fig. 1).

Technic and Method (Preparation of Dogs).—The chronic experiments were carried out as follows: A dog was given an injection of 10 cc. of morphine and atropine solution (¼ grain [0.015 Gm.] of morphine sulfate and $\frac{1}{150}$ grain [0.0004 Gm.] of atropine sulfate per cubic centimeter) twenty to thirty minutes before overinflation was done. When fully asleep the dog was placed on its back on the table. The direct femoral artery blood pressures were taken before, during and after the overinflation. By use of the mouth gag and under direct vision the air tube was introduced into the lower portion of the trachea and the face mask applied.

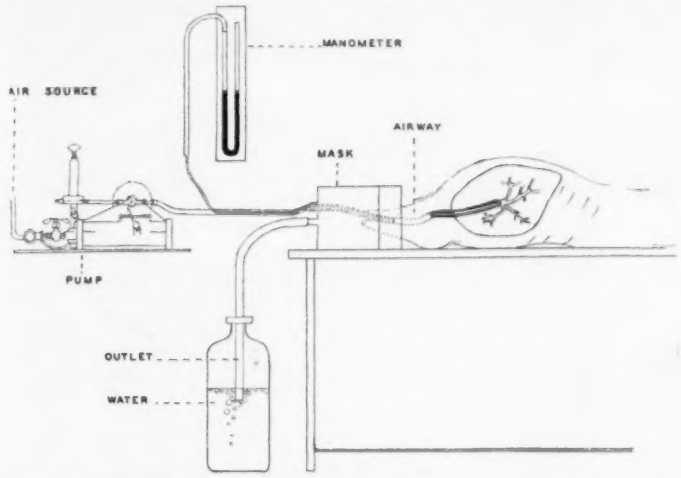

Fig. 1.—Apparatus for overinflation of lungs by intermittent positive pressure.

The air pressure was then turned on and maintained, as described earlier, for fifteen minutes at a maximum of 30 to 35 mm. of mercury at the level of the carina.

After several months of biweekly overinflation in 2 dogs used for chronic experiments (341 and 496) the middle lobe of the right lung was removed for gross and microscopic study and for comparison with the autopsy specimen.

Similar acute experiments were carried out. In these, kymographic tracings were made of the intratracheal air pressure, the pressure in the femoral artery and the pressure in the superior vena cava by means of a seeker introduced through the external jugular vein to a point several centimeters above the right auricle. These pressure studies were made continuously throughout the experiment and long enough afterward to permit observation of recovery phenomena. Pressures above 35 mm. of mercury were apt to cause serious overdistention of the stomach. This was prevented by ligation of the esophagus before starting the experiment. In the chronic experiments air often escaped into the stomach and was evacuated by a stomach tube to permit resumption of normal respiration.

Mortality and Health of Dogs.—In several chronic experiments pressures up to 45 to 50 mm. of mercury were obtained by accident. Two of these dogs (682 and

683) died within a few minutes after the beginning of the experiment. Otherwise, there were no fatalities. Healthy, adult, mongrel dogs were used for the experiments. In several instances they actually gained weight in spite of the frequent doses of morphine and at least two foodless days a week. Morphine addiction, if present at all, was not severe.

Preparation of Specimens.—All autopsy specimens were prepared by removing the lungs from the animal and allowing Kaiserling I solution to gravitate into the trachea and air passages, thus displacing the air; the trachea was then clamped, and the lungs were immersed in the same fluid until thoroughly fixed. Sections were then cut for microscopic study. Special stains for connective and for fibrous tissue as well as the usual hematoxylin and eosin were used in this study.

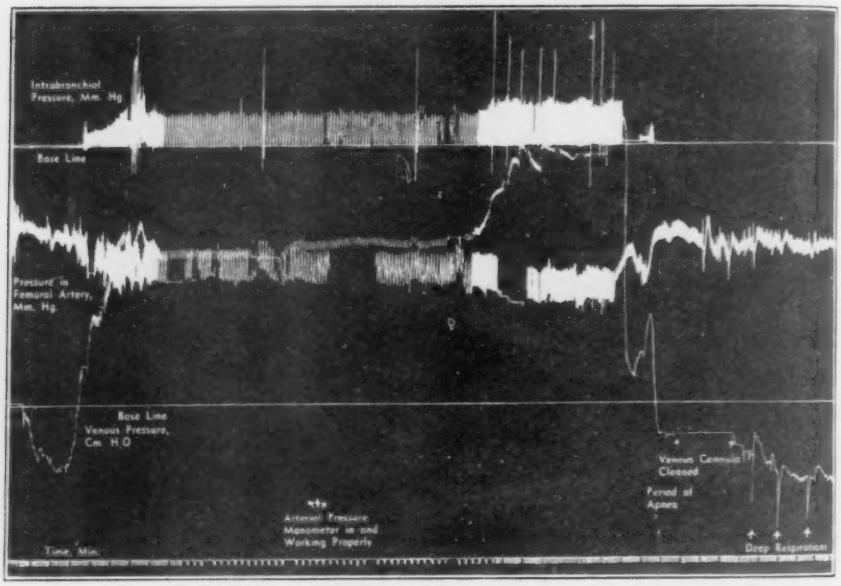

Fig. 2 (dog 341).—Kymogram made during overinflation of lungs by intermittent positive pressure showing the effects of increased intermittent intrabronchial pressure after eleven months of biweekly overinflation. The dog was quiet. The intrabronchial pressure is recorded in millimeters of mercury above; the systemic arterial pressure is recorded in millimeters of mercury in the center, and the venous pressure is recorded in centimeters of water below. The venous pressure rises directly with the intrabronchial pressure, whereas the systemic arterial pressure falls. An intrabronchial pressure of 30 mm. of mercury was maintained during the first ten minutes, and a pressure of 35 mm. of mercury, for six minutes. (Scale, 1:2.88.)

PROTOCOL

Dog 341.—A healthy collie weighing 10.37 Kg. was subjected to increased intrabronchial pressure first on July 9, 1939 and thereafter biweekly until June 8, 1940.

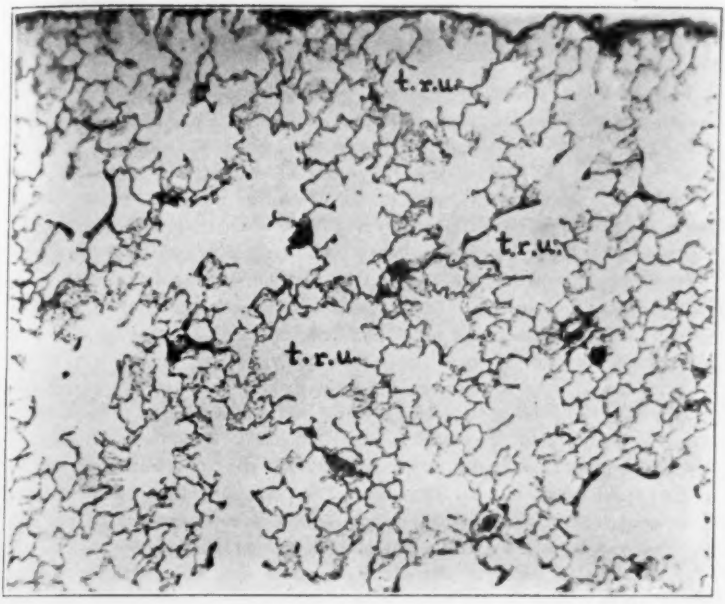

Fig. 3 (dog 341).—Parenchyma of lung at the periphery of a lobe, low magnification. There is moderate dilatation of the terminal respiratory units (*t. r. u.*), with occasional fragmentation of an alveolar wall. No true emphysematous changes are apparent.

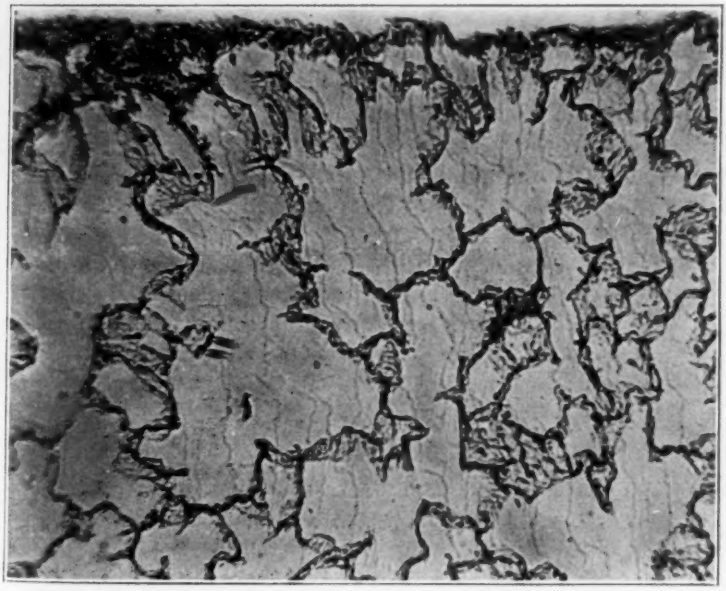

Fig. 4 (dog 341).—Parenchyma of the lung at the periphery of a lobe, high magnification.

On Sept. 11, 1939, after two months of biweekly inflation, the middle lobe of the right lung was removed for gross and microscopic study. Two and one-half weeks (eighteen days) later overinflation by increased pressure was resumed and continued until June 13, 1940, when the dog was killed. Its weight on this date was 10.75 Kg. The dog was given one and one-half times the usual dose of morphine and subjected to the routine fifteen minutes of increased pressure. During this period kymographic pressure studies were made, after which the dog was observed for another twenty minutes (fig. 2). The dog was then electrocuted.[17]

Postmortem Observations.—The trachea was clamped before the chest was opened, at which time the lungs were found fully expanded. Except for one small bandlike adhesion between the lower lobe of the right lung and the site of the lobectomy wound (the middle lobe had been removed) the pleural cavity was normal. There was no gross evidence of mediastinal emphysema. This was in contrast to the presence of mediastinal emphysema in all dogs on which only the acute type of experiment was performed. The heart and lungs appeared normal.

Microscopic Study.—Biopsy Specimen: There was a tendency to dilatation of the terminal respiratory units. The respiratory pores were somewhat larger than in normal lung tissue. There was no dissection or interstitial emphysema as such. When the lobe of the lung was cut across there was little tendency for the parenchyma to collapse. (The parenchyma of the lungs collapsed considerably only after acute experiments when they were cut across after fixation.)

Autopsy Specimen: There was more marked dilatation of the terminal respiratory units, e. g. the alveolar ducts and sacs, with slight tendency to fragmentation of the alveolar walls in some areas. There was slight perivascular and peribronchial interstitial emphysema. This was not as marked as that encountered after the acute experiments. There was no evidence of pulmonary emphysema as defined by destruction of the elastic or the fibrous tissue or of the capillaries of the alveolar walls (figs. 3 and 4).

Comment.—This protocol represents the technical procedures carried out both in the acute and in the chronic type of experiment. It does not represent the physiologic and pathologic findings in the acute type of experiment, as shown in the table.

RESULTS OF EXPERIMENTS

Physiologic Effects of Intermittent Overinflation.—Arterial blood pressures taken five minutes after the institution of positive pressure were an average of 38.3 mm. of mercury lower than the initial pressure, which varied from 90 to 170 mm. of mercury. A partial recovery then occurred during the period of inflation. Pressures taken five minutes after the inflation was discontinued were slightly higher than the initial level. There was a sharp rise to a high level of venous pressure as soon

17. Hrdina, L. S.: Electrocution in Sacrificing Laboratory Animals, J. Lab. & Clin. Med. **15**:86, 1929.

as inflation was begun. The rise varied directly with the intratracheal positive pressure.

Pulse Rate.—There was a tendency toward slight increase in the pulse rate after beginning the inflation, though this was by no means uniformly true. The rate after inflation approximated the initial rate.

Cause of Death.—The 3 acute dogs were electrocuted at the end of the pressure study. Three of the chronic dogs (754, 657 and 341) were likewise studied and killed. Two of the remaining 4 chronic dogs (682 and 683) died during the second inflation, with mediastinal emphysema and air embolism as causes of death. The other 2 chronic dogs died of mediastinal emphysema and spontaneous pneumothorax, 1 (711) after 4 inflations and the other (496) after 39 inflations.

Gross Pathologic Effects.—Two of the acute dogs showed a moderate amount of mediastinal emphysema with no apparent changes in the lungs or heart after inflation for seventy-seven and forty-seven minutes at pressures of 22 and 20 mm. of mercury, respectively, (intrabronchial). One dog (182) after forty-two minutes of inflation at an extreme pressure of 50 mm. of mercury did not show mediastinal emphysema or other apparent change in the lungs or heart.

In the group of 3 chronic dogs studied acutely from thirty-five to forty-eight minutes with intrabronchial pressures varying from 26 to 35 mm. of mercury no mediastinal emphysema or apparent change in the heart or lungs was encountered at autopsy.

Two of the 4 remaining chronic dogs died after the second inflation at an intrabronchial pressure of 35 mm. of mercury with mediastinal emphysema, air embolism and gross subpleural pulmonary hemorrhage.[17a] Another (711) died after the fourth inflation, showing a spontaneous pneumothorax, mediastinal emphysema, air embolism and subpleural hemorrhage. The other dog (496) in this group died of a large pneumothorax at the end of the thirty-ninth inflation at a pressure of 35 mm. of mercury. A slight degree of mediastinal emphysema was also present.

MICROSCOPIC STUDY

Acute Experiments.—The lungs and pleurae of 2 acute dogs (157 and 182) were studied microscopically. The terminal respiratory units, namely, the alveolar ducts and sacs, in some areas, showed slight dilatation. There were also separation and breakdown of the peribronchial and the perivascular tissue, with formation of slitlike air-

17a. Coughing, with temporary elevation of intrabronchial pressure to as high as 50 mm. of mercury was occasionally observed in these experiments.

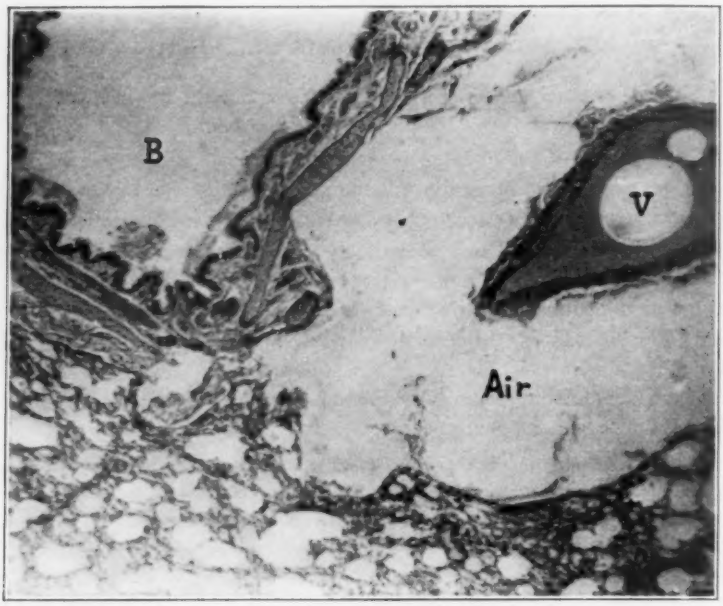

Fig. 5 (dog 683).—Section of lung made after the death of the animal from overinflation. Note the interstitial emphysema (*Air*) separating the bronchial wall (*B*) and the parenchyma from a vessel (*V*), with partial collapse of the last-named structure.

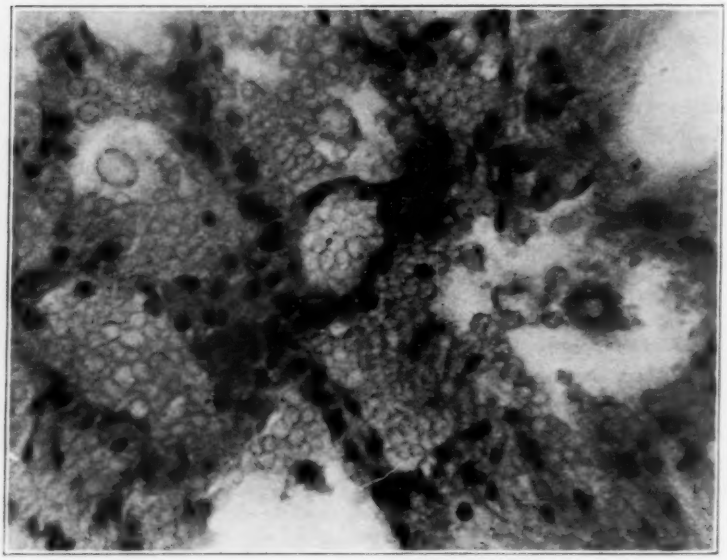

Fig. 6 (dog 683).—Section of lung made after death from overinflation. Note the hemorrhage into the alveoli. (This animal also had air embolism of the pulmonary veins and coronary arteries, besides mediastinal emphysema.)

containing spaces.[5b] The alveoli appeared to be normal, as did the rest of the lung tissue. Sections of lung from dog 182 showed many subpleural macrophages with old pigment. The pleura was much thicker than normal. The latter changes probably explain the failure of interstitial emphysema to develop in this dog.

Chronic Experiments.—Three of the 7 dogs in this group (682, 683 and 711) died during the early part of the experimental period. Microscopically, perivascular and peribronchial interstitial emphysema (fig. 5) was present in sections of the lungs of all 3 dogs. The terminal respiratory units showed changes similar to those seen in the dogs subjected to more acute experiments. However, some evidence of overdistention and rupture of the alveolar walls was present. There was rather marked pulmonary hemorrhage into many of the alveoli, and the perivascular and peribronchial emphysematous spaces (fig. 6). The latter finding was peculiar to these 3 dogs.

In dogs 341 and 496 the middle lobe of the right lung had been removed for microscopic study two and five months, respectively, after the beginning of the experiments. The microscopic sections do not represent the appearance of pulmonary tissue immediately after an overinflation. There was no evidence of perivascular and peribronchial interstitial emphysema. There was some tendency to dilatation of the terminal respiratory units. The alveoli appeared relatively normal except for the respiratory pores of the alveolar walls, which were somewhat larger than those in normal lung tissue.[18]

Three of these 4 chronic dogs (754, 657 and 341) were killed after an acute terminal experiment. Microscopic sections of the lungs of the 3 dogs showed similar changes, the most severe being encountered in dog 657. There was some perivascular and peribronchial interstitial emphysema. This was not as marked as that seen after the acute experiments on dogs 157 and 182. There was more marked dilatation of the terminal respiratory units, with a slight tendency to fragmentation of the alveolar walls in some areas. There was no evidence of pulmonary emphysema as defined by destruction of elastic and fibrous tissue and of the capillaries in the alveolar walls.

The chronic experiment was carried on for seven months (dog 496) and yielded the following microscopic data: On biopsy there was some dilatation of the peripheral air passages but no perivascular or peribronchial interstitial emphysema (fig. 7). These were similar to the

18. Loosli, C. G.: Interalveolar Communications in Normal and in Pathologic Mammalian Lungs, Arch. Path. **24**:743-776 (Dec.) 1937.

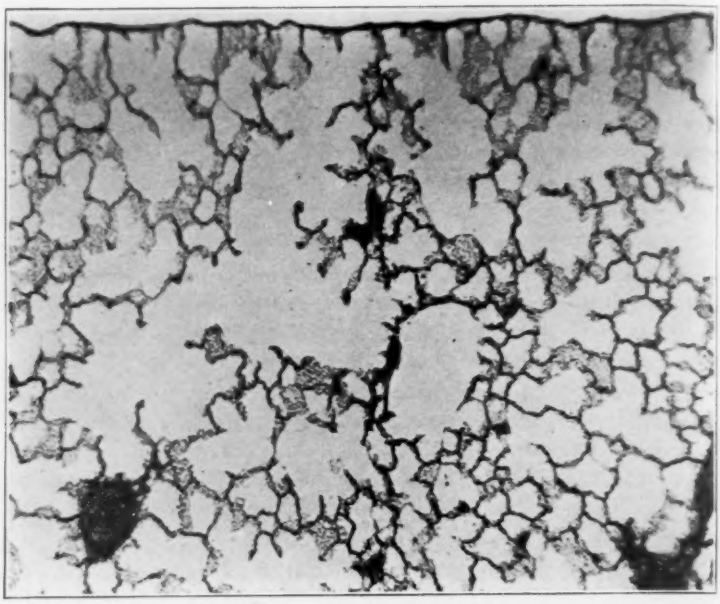

Fig. 7 (dog 496).—Repeated overinflation for seven months was accompanied by spontaneous infection of the lungs during the last two months. A microscopic section of the middle lobe of the right lung removed after five months shows slight dilatation of the terminal respiratory units with no emphysema.

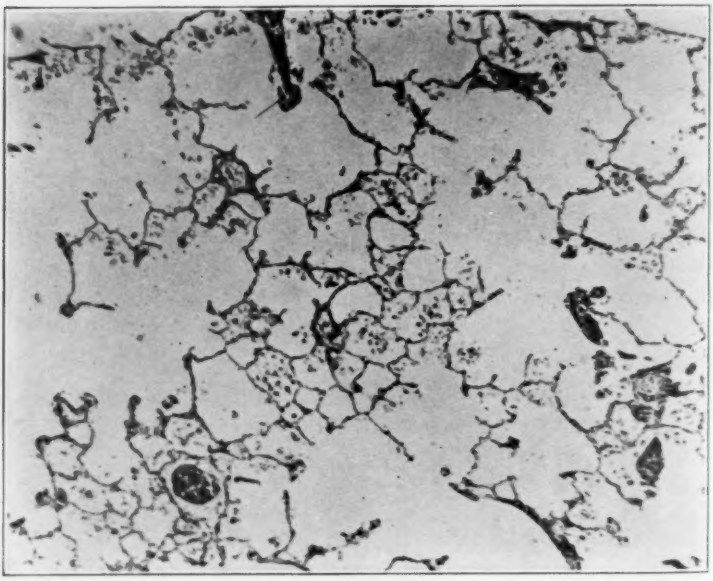

Fig. 8 (dog 496).—Section of the lung of the dog in figure 7 made after death of the animal from a pneumothorax occurring during overinflation. The magnification is the same as that in figure 7. Note the cellular infiltration and the definite emphysematous changes in the parenchyma of the lung.

changes encountered in the biopsy sections of the lung of dog 341. On autopsy the sections showed an old pneumonia. Many of the terminal respiratory units showed extreme dilatation with some destruction of capillaries and other elements of the walls (fig. 8). There were areas of fibrous tissue and unresolved pneumonia with large numbers of lymphocytes and polymorphs (fig. 9).

We believe we should not draw any conclusions from the sections made in this single experiment, since an infection was present and such was not the case in any other dog.[19]

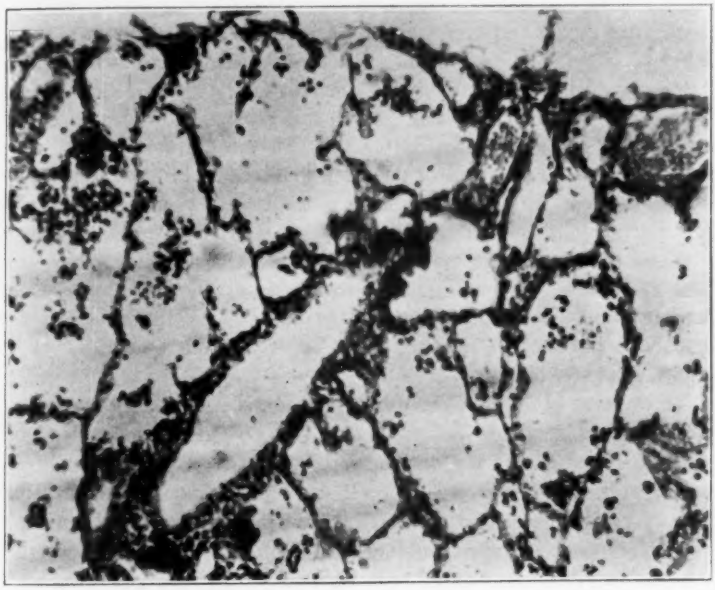

Fig. 9 (dog 496).—A portion of the area comprising figure 8 more highly magnified and showing diffuse pneumonitis.

COMMENT

In cases of clinical emphysema there is usually enlargement of the thorax together with a history of a chronic cough, with or without asthmatic symptoms. The pathologic condition is usually characterized microscopically by evidence of chronic inflammation attending the emphysematous changes, i. e., destruction of elastic and fibrous tissue

19. Drs. C. C. Macklin and Clayton G. Loosli gave criticism in the interpretation of the microscopic observations.

and the capillary structure of the alveolar walls. The degree of these inflammatory changes depends on the clinical course of the disease prior to the time of death, i. e., acute or chronic.

The results of these experiments are those following overdistention of the lung simulating repeated asthmatic attacks extending over several months. The elements of enlargement of the thorax and infection are eliminated with the exception of the inflammatory changes in dog 496. This pressure phenomenon in itself appears to have failed in the production of emphysema, although repeated overdistention for fifteen minutes biweekly over a period as long as eleven months was carried out. There was, however, moderate dilatation of the terminal respiratory units, i. e., the alveolar ducts and sacs, but no microscopic destruction of alveolar elements. The acute experiments, except in 1 old dog, resulted in interstitial and mediastinal emphysema, whereas in the chronic experiments which were terminated by acute study this phenomenon was absent or less marked. The explanation for this difference was probably on a basis of the repeated injury of the interstitial tissue during overinflation with subsequent fibrosis in the latter experiments. In sections of normal lung parenchyma the walls of the alveolar ducts between the alveolar sacs and the alveoli are made up of muscle cells and elastic and collagenous fibers. The latter elements appear as short knobs or clubs running parallel to the long axis of the duct.[20] We believe that these have been erroneously interpreted by some authors[21] as evidence of emphysematous changes.

In the case of dog 496, in which pneumonia was present, there was insufficient evidence to warrant drawing conclusions. It is most suggestive that the factor of infection when added to repeated overdistention is significant in the production of pulmonary emphysema. This is receiving further attention at the present time. Microscopic sections showing pulmonary emphysema resulting from tracheal obstruction and overdistention which have been presented by another author[14] strongly suggest a combination of infection and overdistention as the etiologic factor.

Pressures.—Periods of overinflation were routinely accompanied by a diminution in the systemic blood pressure to such a level that cyanosis was occasionally observed. This is similar to that sometimes seen clinically during asthmatic attacks. Accompanying this fall in systemic blood pressure was a marked rise in the peripheral venous pressure,

20. Maximow, A. A., and Bloom, W.: Textbook of Histology, ed. 3, Philadelphia, W. B. Saunders Company, 1938, p. 448.

21. Longacre, J. J., and Johansmann, R.: An Experimental Study of the Fate of the Remaining Lung Following Total Pneumonectomy, J. Thoracic Surg. **10**: 131-149, 1940.

indicating the increased resistance to the circulation in the lung and also the load placed on the right side of the heart during overdistention. This is similar to the changes occurring during an asthmatic attack and explains the development of hypertrophy and failure of the right side of the heart in persons with chronic asthma.

Mediastinal emphysema, air embolism and subpleural (and parenchymal) hemorrhage developed during overdistention in 2, or 22.2 per cent, of 9 dogs. This phenomenon might explain the cause of death in some asthmatic persons in whom heart failure or other definite cause is not evident.

Biweekly pulmonary overinflation alone with a pressure of 35 mm. of mercury over periods as long as eleven months failed to produce true emphysema in dogs.

The pressures used for overinflation were sufficient to cause marked lowering of the systemic arterial pressure and marked elevation of peripheral venous pressure and in 2 cases pulmonary air embolism and hemorrhage into the pulmonary parenchyma.

There were emphysematous changes of the parenchyma of the lung in 1 dog in which the factor of infection was added to that of overdistention.

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GUMMATOUS AORTITIS

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AND

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Syphilitic disease of the aorta may occur in either of two forms, (*a*) as a productive scar-forming type of chronic aortitis or (*b*) as gummatous aortitis. The former is the usual manifestation of cardiovascular syphilis. Gummatous lesions of the aorta, on the other hand, are rarely observed, and this type of aortitis has not been studied extensively. It is the purpose of this communication to describe the clinical and the morphologic features of gummatous aortitis and to define the differential characteristics of this disease in relation to other diseases of the aorta.

This study was stimulated by observations made in the following 3 cases, which we are reporting in detail.

REPORT OF THREE CASES

CASE 1.—C. C., a 35 year old Italian-born housewife, was admitted to the Boston City Hospital for the third time on Nov. 14, 1935. On entrance she was in a state of acute pulmonary edema, manifested by frothy bloody sputum, cyanosis, profuse perspiration and mild delirium. She did not respond to emergency treatment and died shortly after admission.

The patient had been well until July 1934, when she had begun to notice shortness of breath on mild exertion. Since that time she had also had a sense of constriction in the precordial region when she walked, but never while at rest. This distress would pass away soon after the cessation of activity. For approximately the same period (seventeen months) she would feel well on retiring, only to be awakened by severe attacks of nocturnal dyspnea which recurred three or four times during the night. Until six months before entry she had not noticed edema of dependent parts. Although a dry cough had been present, she had never noticed any blood-flecked sputum.

There was no history of pains in the joints, chorea or an unusual number of attacks of sore throat, although her tonsils had been removed the year before. She had undergone a cesarean section in 1931 and stated that at that time her blood was "all right." The patient stated, however, that she had had "bad blood" since the age of 20 and was treated with "shots" at that time. In January 1934 the patient

† Deceased.

From the Mallory Institute of Pathology of the Boston City Hospital and the Medical Clinic of the Peter Bent Brigham Hospital.

was delivered of a premature baby, at which time she was found to have a positive serologic reaction for syphilis. She was referred to the outpatient department of the Massachusetts General Hospital for treatment. After four intramuscular and two intravenous injections of an antisyphilitic compound she did not return to the clinic.

The patient was admitted to the Boston City Hospital for the first time on July 6, 1934, with the complaint of inability to sleep because of attacks of "shortness of breath." Her ankles were markedly swollen. She had been nauseated but had not vomited. On conservative treatment the patient improved rapidly and was discharged on the twentieth day after admission, symptom free, only to return to the outpatient department three months later with the same complaint of inability to sleep because of choking attacks. She had been only "fairly well" since her discharge, even though she was on a restricted regimen and was taking digitalis. In the hospital she again improved and was discharged on the twenty-sixth day after entry with the recommendation of convalescent care, which she refused. It was on the fourth day after discharge that the patient returned to the hospital moribund and died in an attack of cardiac asthma with pulmonary edema.

Clinical and Laboratory Data.—The essential findings one month before her fatal attack included the following data: The patient was sallow, tired-appearing and fairly well developed and nourished. She was sitting upright in bed, breathing with difficulty. Her eyes, ears, nose and throat were not remarkable. Moderate venous congestion was present in the neck. There was flatness to percussion in the bases of both lungs, extending to the eighth vertebral spine on the left side, with flatness and markedly diminished breath sounds on the right side. The heart was greatly enlarged, with the left border of dulness in the anterior axillary line; the right border of dulness extended 4 cm. to the right of the sternum. At the apex the heart sounds were almost entirely replaced by continuous swishing systolic and diastolic murmurs; at the level of the second rib on the right there were a loud diastolic murmur replacing the second sound and a softer "hissing" systolic murmur. The aortic diastolic murmur was transmitted from the base of the heart almost to the apex. Along the left border of the sternum an inconstant thrill, diastolic in time, was also noted. There was a collapsing type of pulse, and the blood pressure was 150 mm. of mercury systolic and 50 mm. diastolic. The liver was slightly tender and palpable 2 fingerbreadths below the costal margin. The spleen was firm, nontender and palpable 3 fingerbreadths below the left costal margin. Otherwise the abdomen was normal. There was slight pitting edema below the knees. At the time of admission the patient was afebrile; the pulse rate was 85 per minute and the respiratory rate 20 to 24 per minute.

The urinary sediment was essentially normal. The specific gravity ranged from 1.007 to 1.019. The red cell count was 3,970,000 per cubic millimeter; the hemoglobin concentration, 86 per cent. The white cell count was 4,000 per cubic millimeter; the differential count showed 61 per cent polymorphonuclears, 32 per cent lymphocytes and 7 per cent monocytes. Kahn and Hinton reactions of the blood were positive. Per hundred cubic centimeters, the blood contained 35 mg. of nonprotein nitrogen and 5 Gm. of total protein and the albumin-globulin ratio was 2 to 1. A roentgenogram revealed the heart to be enlarged both to the right and to the left. On fluoroscopic examination there was a slight increase in the size of the right auricle, which appeared to pulsate during ventricular systole; therefore the presence of a tricuspid regurgitation was suspected. The

lungs were within normal limits. The electrocardiogram showed a normal rhythm, a rate of 100 per minute, a PR interval of sixteen hundredths of a second and a QRS interval of twelve hundredths of a second. The QRS was slurred in all leads. The T wave was upright in lead I, diphasic in lead II and inverted in lead III. The axis was normal. The interpretation was intraventricular block.

In addition to the usual treatment for congestive failure of the circulation, the patient was given potassium iodide and a few injections of an antisyphilitic compound.

Diagnosis: The diagnoses at the time of death were syphilitic heart disease with aortitis, aortic regurgitation and probably narrowing of the mouth of the coronary arteries; congestive heart failure with slight peripheral edema, chronic passive congestion of the liver and left hydrothorax; syphilitic splenomegaly, and cardiac asthma with terminal pulmonary edema.

Necropsy.—The heart (with part of the aorta) weighed 600 Gm. The epicardium was smooth and glistening. The myocardium was deep red and moderately firm. There was some hypertrophy of the left ventricular wall and dilatation of all the chambers. The valves of the right side of the heart were normal. There was slight thickening and shortening of the chordae tendineae of the median cusp of the mitral valve associated with lengthening of the corresponding papillary muscles. There were pearly gray, glistening, translucent, moderately firm nodules 1 to 3 mm. in diameter along the line of closure of the mitral valve. There was no scarring of the papillary muscles.

All of the aortic cusps were gray, firm and thickened, with an increase in thickness at the free margins. The cusps were contracted, and the commissures of all were separated. This was most marked between the anterior and the right posterior cusp, which were separated by a distance of 0.8 cm. The right half of the anterior cusp was detached at its base, allowing the cusp to flap as a tongue-like process. There was transverse white thickening of the ventricular endocardium beneath the anterior aortic cusp where it was detached. The endocardium of the left auricle and the left ventricle was thickened.

Valvular measurements were as follows: tricuspid 14.3 cm., pulmonary 8.5 cm., mitral 10.3 cm. and aortic 7.5 cm. The thickness of the left ventricle was 1.6 cm. and that of the right ventricle 0.3 cm.

The first 2.5 cm. of the ascending aorta was distinctly thickened by moderately firm tissue, the surface of which was pitted and gray except for one yellow area 1 cm. in diameter where the surface of the aorta was depressed (fig. 1). The right coronary opening ran through this area and was closed. The orifice of the left coronary artery lay 1.5 cm. above the level of the opening of the right one. There was slight narrowing of the lumen of the left coronary artery by heaping up of pearly gray tissue around its lower half. The coronary arteries beyond their orifices were normal. At the beginning of the aortic arch there was a round swelling 1.5 cm. in diameter which projected 0.4 cm. above the intimal surface. The surface was gray and pitted. The cut surface revealed a gray, glistening tissue, replacing the intima and apparently the media. Slightly yellow intimal thickening was encountered around the orifices of the great vessels from the aortic arch. In the descending thoracic aorta there were a few linear elevations similar in appearance to the round elevation at the beginning of the arch. Otherwise the aorta appeared normal and elastic and the intima smooth and glistening. The result of the examination of other organs was unessential.

Anatomic Diagnosis: The anatomic diagnoses were aortic endocarditis, probably syphilitic; mitral rheumatic valvulitis; complete occlusion of the right coronary artery and partial occlusion of the left one; focal aortitis, probably syphilitic; pulmonary congestion and edema, and bilateral hydrothorax.

Histologic Examination.—Heart: The muscle fibers were hypertrophied. A few small scars were scattered through the myocardium. Both the epicardium and the endocardium contained a small number of lymphocytes.

Mitral Valve: The leaflets were somewhat thickened due to rather cellular and edematous connective tissue.

Aortic Valve: The cusps were markedly thickened because of a large amount of relatively acellular, somewhat hyaline collagen. Vascular spaces were present, and about them occurred lymphocytes and plasma cells in varying numbers. The

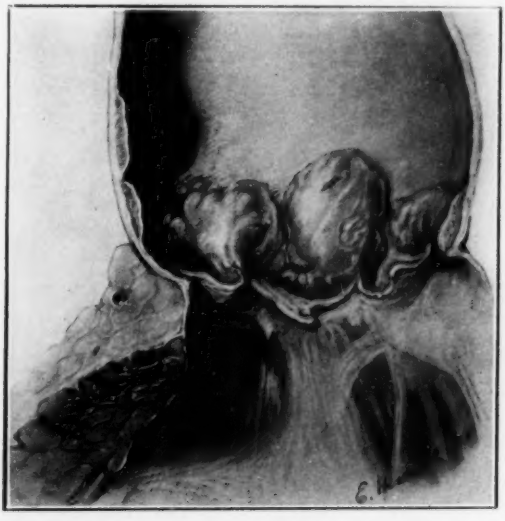

Fig. 1 (case 1).—The aortic valve and adjacent aorta and left ventricle. The aortic leaflets are thickened and shrunken. Above the cusps are projecting nodular areas which represent the regions of the aorta involved by the gummatous mesaortitis.

base of the valve and the adjacent endocardium showed a type of thickening similar to that of the cusps.

Ascending Aorta: The intima showed a nodular increase in connective tissue, some of which was evidently recently formed and quite cellular, while other areas consisted of dense collagen. In the thickened areas a few small blood vessels were present, and about some of them were occasional lymphocytes and plasma cells. The media contained foci of necrosis. At the periphery of such necrotic areas there was vascular connective tissue, heavily infiltrated with lymphocytes, plasma cells and some giant cells. In one or two such areas there were also some polymorphonuclear leukocytes. Elsewhere there were foci of extensive

scarring. Such scars were made up of vascular, rather cellular connective tissue infiltrated with plasma cells and lymphocytes. The adventitia showed pronounced thickening with dense connective tissue which was infiltrated with lymphocytes

Fig. 2 (case 1).—The media, showing an area of necrosis. Adjacent to this area is a focus of vascular connective tissue infiltrated with lymphocytes, plasma cells and some giant cells.

and plasma cells. The arteries showed a slight to marked degree of endarteritis obliterans.

Histologic Diagnosis: The histologic diagnoses were gummatous mesaortitis and healed endocarditis of the mitral and the aortic valve.

CASE 2.—J. M., a 35 year old Irish-American chauffeur, was admitted to the Boston City Hospital on June 9, 1936, with chief complaints of severe dyspnea, cough and edema of the legs. This was his ninth hospital admission since 1930.

At the age of 8 the patient had suffered from a severe attack of migrating polyarthritis, manifested by swollen and painful joints, sore throat, fever and nodules over his legs. He was kept in bed about three months. Between the ages of 8 and 14 he had been well except for occasional mild subacute painful swelling of certain joints. At the age of 14 he had had a short but severe attack of rheumatic fever and was in bed for fourteen days. During the following sixteen years he had felt well. In 1930, at the age of 30, he had had another attack of rheumatic fever, with malaise, fever, anorexia and pains in the joints, and had entered the hospital. The diagnoses were chronic rheumatic heart disease with aortic stenosis and insufficiency, mitral stenosis, cardiac decompensation, angina pectoris and Schönlein's purpura. The patient improved markedly under treatment.

In 1932 he had reentered the hospital, and in view of a positive reaction of the blood for syphilis, a syphilitic causation of the heart disease had been suggested. The suspicion was strengthened by finding gummatous lesions involving the soft palate and the fauces. The patient was given partial antisyphilitic treatment. On each of seven subsequent admissions, in addition to the rheumatic, the question of syphilitic, causation of the heart disease had been discussed. The patient had entered the hospital on each occasion because of severe nocturnal paroxysmal dyspnea associated with angina pectoris.

The family history was noncontributory. The patient had married in 1925 and become divorced in 1927. His wife had had one miscarriage.

Clinical and Laboratory Data.—During the last admission, in 1936, the essential findings included the following data: The patient was in a high orthopneic position. His expression was anxious, and he was sweating profusely. Scarred atrophic areas were scattered on the fundi of both eyes. The nasal septum was perforated. Punched-out and scarred areas were present over the soft palate. The arteries of the neck showed pronounced pulsation. There was a severe, loud, rough systolic murmur over the carotid arteries. The veins of the neck were not distended. There was a prominent systolic heave over the left side of the thorax, and all the intercostal arteries were pulsating. The apical impulse was in the fifth interspace in the midaxillary line. There was a marked thrill over the second right intercostal space. At the apex a loud crescendo presystolic murmur was heard. This was followed by a rough systolic, and by a long blowing softer diastolic, murmur. All three murmurs were well transmitted into the axilla. Over the aortic area there was a rough loud systolic murmur corresponding to a systolic thrill and a blowing diastolic murmur. The diastolic murmur was heard with clarity all over the precordium. The aortic systolic murmur was transmitted to the neck. The pulses were of water-hammer character, and a clear Duroziez murmur was present. The arterial pressure in the arm was 155 mm. systolic and 45 mm. diastolic and in the leg 230 mm. systolic and 40 mm. diastolic, measured in millimeters of mercury. No other abnormalities were present.

During his last stay in the hospital the urine was normal. There was no anemia or leukocytosis. The Hinton reaction of the blood was positive. Electrocardiograms revealed no change from the condition observed on previous admissions.

The patient improved under treatment, but an attack of acute dyspnea and cyanosis developed, and he died within five minutes after the onset of the attack.

Diagnosis: The diagnoses included rheumatic and syphilitic heart disease with aortic stenosis and insufficiency, mitral stenosis and insufficiency, congestive failure of the circulation, angina pectoris, syphilitic chorioretinitis and tertiary syphilis.

Necropsy.—The pericardial cavity was completely obliterated by old fibrous adhesions, which after removal left a rough and irregularly hemorrhagic visceral pericardium. The heart weighed 780 Gm. The pulmonary, tricuspid and mitral valves were entirely normal. The left ventricle was markedly dilated and the wall hypertrophied, with a thickness of 2.2 cm. About 1 to 2 cm. below the aortic valve was a linear fibrous thickening (Zahn's pocket). The aortic valve was dilated and showed marked thickening of the free margins of the cusps. In addition, between the left anterior and the posterior cusp there was about 0.15 cm. of separation, while the remaining adjacent portions of the cusps were fused. This was most

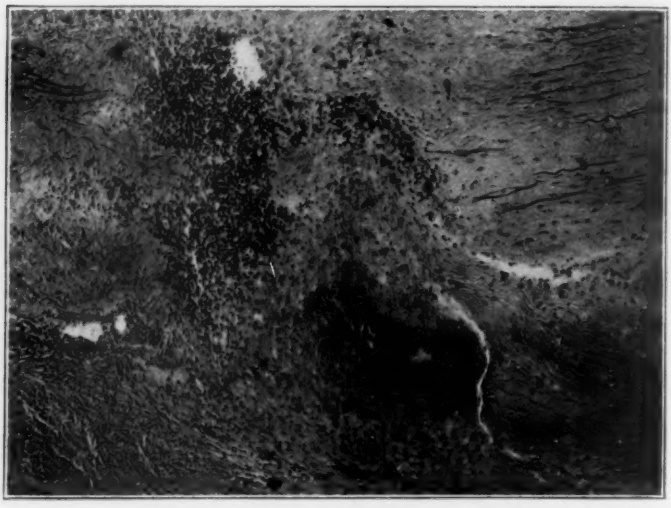

Fig. 3 (case 2).—Gummatous mesaortitis. There is a large area of destruction of the media with a focus of caseation necrosis. The remainder of the defect in the media is filled with connective tissue densely infiltrated with lymphocytes, plasma cells and giant cells.

marked between the right posterior and the anterior cusp. The coronary orifices were widely patent. The right ventricular wall was moderately hypertrophied and measured 0.5 cm. The circumferences of the cardiac orifices were as follows: tricuspid valve 11.6 cm., pulmonary valve 7.5 cm., mitral valve 11.2 cm. and aortic valve 8.5 cm.

The aorta was normal except for the ascending portion of the arch. Here there were elevated, irregular, flat, yellowish white and somewhat soft patches 4 to 6 mm. in diameter. The rest of the aorta was essentially normal.

Anatomic Diagnosis: The anatomic diagnoses were syphilitic aortitis with involvement of the aortic valve, healed aortic valvulitis, cardiac dilatation and hypertrophy and pulmonary congestion and edema.

Histologic Examination.—Heart: The muscle fibers were hypertrophied. Both the epicardium and the endocardium contained an increased amount of collagen. In the endocardium were several focal collections of large, mononuclear cells with basophilic cytoplasm. These cells were arranged tangentially along strands of collagen. There were some lymphocytes at the periphery of these areas. Similar smaller focal collections of these large basophilic cells could be found in the region of the blood vessels in the myocardium. These focal lesions had all the characteristics of Aschoff bodies. There were in addition scattered polymorphonuclear leukocytes about the myocardial vessels.

Aortic Valve: The cusps contained a large amount of acellular collagen. Blood vessels were fairly numerous and showed a varying degree of perivascular infiltration with lymphocytes and histiocytes. In one cusp near the base there was an area of necrosis. Surrounding this were numerous histiocytes and giant cells. The necrotic material contained nuclear debris.

Aorta: The intima showed marked thickening with cellular connective tissue which was infiltrated with some fatty macrophages and lymphocytes. The media was interrupted by scars made up of vascular connective tissue infiltrated with lymphocytes and plasma cells. In addition, there were fairly numerous foci of necrosis. These necrotic areas were surrounded by large mononuclear cells, giant cells, lymphocytes and plasma cells. The adventitia was thickened and contained bundles of rather dense collagen. The vasa vasorum showed varying degrees of endarteritis obliterans, and many had a perivascular infiltration of lymphocytes and plasma cells (fig. 3). Sections of the heart, the aortic valve and the aorta stained by Levaditi's method gave negative results. The rest of the histologic data were unessential.

Histologic Diagnosis: The histologic diagnoses were gummatous mesaortitis, healed endocarditis and gummatous endocarditis of the aortic valve and rheumatic myocarditis.

Case 3.—The specimens in this case, in which the patient was a 42 year old housewife who died suddenly, were furnished us by Dr. Timothy Leary, Medical Examiner for Suffolk County, Boston. This patient had enjoyed good health except for complaints of soreness over the epigastrium and pains about the heart for two years previous to her sudden death. She had walked into the house of friends, vomited blood and fallen to the floor unconscious. She was rushed to the hospital but was dead on arrival.

Necropsy.—The heart weighed 220 Gm. The myocardium was brownish red. All the valves were normal. The measurements were as follows: tricuspid valve 10.5 cm., pulmonary valve 5.4 cm., mitral valve 9.1 cm. and aortic valve 5.2 cm. The thickness of the left ventricle was 1.7 cm. and that of the right ventricle 0.3 cm. There was a marked narrowing of the orifices of both the right and the left coronary artery.

The proximal 5 cm. of the aorta showed a rough intima with numerous slightly raised, pearly gray nodules which varied from 3.0 to 8.0 mm. in diameter. Between the aorta and the pulmonary artery was a mass of firm tissue, measuring 3.0 by 2.0 by 1.5 cm. On section this tissue was grayish in color with yellowish areas. This mass protruded into the lumen of the pulmonary artery at several points, extending 2.0 to 4.0 mm. above the intimal surface, which was apparently intact. These projections had a smooth, lobulated surface and were yellowish white. There was a small, saccular aneurysm of the aortic arch in its superior posterior portion. This

aneurysm lay between the innominate and the left common carotid artery (fig. 4). A short tract led from the depth of this aneurysm into the trachea, 2 cm. above its bifurcation. The tracheal mucosa in this region was greenish red and was ulcerated over an area 0.8 cm. in diameter, although the perforation was pinpoint in size (fig. 5). The external surface of the aortic arch was covered with firm gray tissue. The descending aorta was normal save for a few small yellowish plaques.

Fig. 4 (case 3).—The descending aorta and an aneurysm of the transverse portion. Both above and below the opening of the aneurysm is seen an extensive granulomatous involvement of the mediastinal tissues with numerous gummas.

The right lung weighed 550 Gm. The external surface was dark red, smooth and glistening. The upper lobe had a firm, rubbery consistency. Its cut surface was dark red, and a small amount of pink, frothy fluid could be expressed. The middle and lower lobes were essentially similar to the upper lobe.

Anatomic Diagnosis: The anatomic diagnoses were aneurysm of the aorta with perforation into the trachea and syphilitic aortitis.

Histologic Examination.—The myocardium was normal. Sections through the left coronary artery showed some fibrous thickening of the intima.

There were foci of necrosis in the media of the ascending aorta typical of gummatous mesaortitis, as described in the 2 preceding cases. The adventitia showed fibrous thickening with marked perivascular infiltrations of lymphocytes and plasma cells around the vasa vasorum, which showed various degrees of endarteritis obliterans. The intima exhibited atheromatous changes. Sections of the aneurysm at its point of rupture into the trachea showed extensive necrosis consistent with gumma. The trachea at this point exhibited thickening of the submucosa due to

Fig. 5 (case 3).—The trachea, showing the point of rupture of the aortic aneurysm.

granulation tissue and an infiltration of numerous lymphocytes and plasma cells. There was, in addition, an area of necrosis with ulceration of the overlying epithelium.

The mass of tissue lying between the aorta and the pulmonary artery was composed of granulation tissue with numerous areas of infarct necrosis. Giant cells were numerous, and there was a marked infiltration of lymphocytes and plasma cells. This granulomatous process had invaded and destroyed the adventitia and the media and had involved to a marked degree the intima of the pulmonary artery. The masses projecting into the lumen of the pulmonary artery

described in the gross examination were composed of this gummatous granulation tissue. The endothelium lining the vessel was intact. The vessel wall where it was not invaded by this granulomatous tissue showed no changes.

Histologic Diagnosis: The microscopic diagnoses were gummatous mesaortitis and gummatous mediastinitis with involvement of the pulmonary artery.

MATERIAL STUDIED AND ADDITIONAL CASES

As a result of the study of these 3 cases a systematic study of gummatous aortitis was undertaken. The material used came from the departments of pathology of the Boston City Hospital and the Massachusetts General Hospital. A total of 360 cases of syphilitic aortitis were studied, 186 cases from the former, and 174 from the latter, institution. All cases in which necrosis was evident were investigated in detail. Gummatous aortitis, as its name implies, is characterized by gumma formation, usually in the media. In our series the gummas were usually of miliary type and could be definitely recognized only microscopically. They occurred as areas of necrosis involving both muscle and elastic tissues. The necroses either were of the infarct type, i. e., the outlines of the preexisting structures could be recognized in the necrotic areas, or were composed of structureless material containing nuclear debris. Calcification of such necrotic foci did not occur. The form of the medial gummas conformed to the structures of the media, being roughly quadrangular or oval in shape. At the periphery of such gummas were broad sheets of vascular granulation tissue which was heavily infiltrated with lymphocytes, plasma cells and some large mononuclear cells. Giant cells were present, usually in close proximity to the necrotic material.

The adventitia showed marked thickening due to increased connective tissue, which was infiltrated with numerous lymphocytes and plasma cells, especially in the neighborhood of the vasa vasorum. These vessels often showed varying degrees of endarteritis obliterans. Occasionally gumma formation occurred in the adventitia (fig. 6). The intima usually showed varying degrees of fibrosis, often focal in distribution.

The atheromatous changes observed in our large group of cases of chronic syphilitic aortitis were usually pronounced over the parts affected by syphilis, suggesting that the syphilitic process had enhanced the development of intimal atheromas. A similar view has been expressed recently by Leary.[1]

There were 8 cases of gummatous aortitis in 360 cases of aortitis. In 2 additional cases the histologic changes were suggestive, but no definite diagnosis could be made. Obviously, the frequency ratio of 1:45 must be considered as minimal, in view of the fact that the finding

1. Leary, T.: Syphilitic Aortitis as Cause of Sudden Death, New England J. Med. **223**:789-793, 1940.

of gummas was not based on a study of systematic serial sections of the arch of the aorta.

The ages of the patients in these 8 cases of gummatous aortitis varied between 32 and 59. Five patients were men, and 3 were women. Five of the patients had aortic insufficiency. Paroxysmal cardiac dyspnea was present in 5 cases. The immediate cause of death was usually pulmonary edema. It is of especial interest that in 1 case a patient had also suffered from rheumatic fever.

The clinical features in these cases of gummatous aortitis are not specific or characteristic. The clinical manifestations, such as dyspnea, orthopnea, precordial distress, cardiac asthma and pulmonary edema,

Fig. 6.—A gumma in the adventitia of the aorta.

are attributable to the presence of aortic insufficiency or narrowing or occlusion of the coronary arteries. The two last-named changes may be caused by the gummatous syphilitic lesion, as was true in 1 of the cases observed by us (case 1). Clinical diagnosis of gummatous aortitis is difficult or even not feasible. The coexistent rheumatic condition, however, may raise suspicion, for it seems more than a coincidence that in 3 of the 11 cases studied by us the patients had also suffered from rheumatic fever.

In 3 additional cases of chronic syphilitic aortitis massive destruction of the aortic wall was present. These lesions contained polymorphonuclear leukocytic infiltration, a picture not unlike an abscess. In these cases the lesions were not considered as being gummatous. Three possibilities of causation were considered in these cases: first, that the acute destructive lesions were the result of syphilis alone; second, that

they were the result of a secondary invading infection superimposed on syphilitic aortitis, as reported by Rappaport [2] and by Saphir and Cooper,[3] and third, that they were unrelated to syphilis.

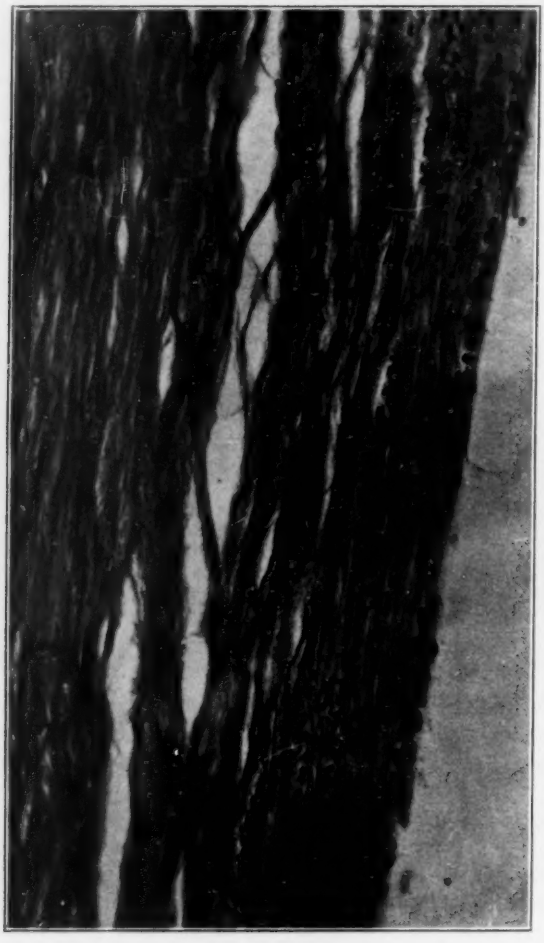

Fig. 7.—Acute aortitis. Infiltration of the intima with polymorphonuclear leukocytes is evident.

In order to determine whether similar acute abscess-like lesions are found in aortas of nonsyphilitic subjects, the records and the histologic

2. Rappaport, B. Z.: Primary Acute Aortitis, Arch. Path. **2**:653-658 (Nov.) 1926.

sections of the aortas in 224 control cases in which death occurred from a variety of causes were examined for focal acute aortitis of the type observed in these cases of syphilis. Six cases of acute nonsyphilitic aortitis were collected. In 1 case it occurred in a patient with mediastinitis, in 4 in patients with medionecrosis idiopathica cystica and in 1 in a patient with lymphatic leukemia (fig. 7). It is therefore concluded that the occurrence of such acute abscess-like lesions of the aorta is unrelated to syphilitic aortitis, though it is probable that syphilitic aortitis and other chronic conditions in the aorta predispose to the development of secondary acute aortitis.

DIFFERENTIAL MORPHOLOGIC CHARACTERISTICS OF ACUTE LESIONS OF THE AORTA

There are a number of other acute diseases of the aorta, which it is essential to differentiate from gummatous aortitis.

Acute Bacterial Aortitis.—Acute lesions with abscess formation of the intima of the aorta are on the whole uncommon and when they do occur are usually secondary to infectious lesions of the cardiovascular system elsewhere, most commonly endocarditis. An extremely rare form, termed primary acute aortitis by Rappaport,[2] occurs without other infectious lesions of the vascular system being present. It is generally agreed that a preexisting lesion of the aorta, especially an atherosclerotic lesion, predisposes to bacterial invasion of the intima. However, Rappaport [2] and Saphir and Cooper [3] have reported single cases of acute aortitis superimposed on syphilitic aortitis. The occurrence of acute bacterial aortitis superimposed on atherosclerosis or on syphilitic aortitis may be looked on as being analogous to the occurrence of abscesses in previously damaged or diseased myocardium or voluntary muscle.[4] On the basis of a study of the literature, Rappaport stated that previous pathologic changes, whether atherosclerotic or syphilitic, predispose to acute infection of the wall of the aorta either through direct implantation of its surface or through the vasa vasorum. However, the presence of a concomitant acute inflammation does not influence the histologic picture of syphilitic aortitis.

In our series we encountered 1 case of acute bacterial aortitis secondary to pneumococcic endocarditis of the tricuspid valve, occurring in an atheromatous plaque (fig. 8).

Rheumatic Aortitis.—The lesions of rheumatic fever usually are located in the adventitia and media but may also involve the intima. In the acute stage the vasa vasorum show swelling of their endothelium,

3. Saphir, O., and Cooper, G. W.: Acute Suppurative Aortitis Superimposed on Syphilitic Aortitis, Arch. Path. **4**:543-545 (Oct.) 1927.

4. Weiss, S., and Wilkins, R. W.: Myocardial Abscess with Perforation of the Heart, Am. J. M. Sc. **194**:199-204, 1937.

and there is a scattered infiltration in the adventitia of lymphocytes, plasma cells and large mononuclear cells, some of which are Aschoff cells. In the media at this stage numerous Aschoff cells may be found,

Fig. 8.—Acute bacterial aortitis. Spaces in the intima contain masses of pneumococci.

arranged in rows between the elastic fibers. The nutrient vessels in the media show intimal swelling. There is a varying amount of perivascular infiltration of lymphocytes, plasma cells, polymorphonuclear leukocytes

and large mononuclear cells. The collagen adjacent to the vessels shows swelling and degeneration.

In the later active, or in the healed, stage the connective tissue of the adventitia is thickened and dense and contains scattered lymphocytes and plasma cells. In addition, Aschoff cells may be present and may have a focal arrangement suggesting Aschoff nodules. In the media there are avascular, collagenous scars in the areas in which the nutrient vessels normally occur, namely, the outer third.

Tuberculosis of the Aorta.—This is on the whole an uncommon lesion of the aorta. Usually the involvement occurs from extension of a tuberculous process from neighboring structures. More rarely it arises in the intima from a hematogenous infection. Histologically, the lesions show the usual picture of tuberculosis, either the caseous or the miliary type.

Atherosclerotic Necrosis.—The necrosis associated with atherosclerosis is situated primarily in the intima, although some extension into the adjacent media may occur. The necrotic areas either represent the late stage of a previously lipoid-filled focus or occur in the deeper portions of healed, fibrous plaques. The lesions appear under low magnification as pale, essentially unstained areas. Under high magnification these areas are found to consist of anuclear material with no definite structure. Clefts representing cholesterol crystals are frequently present in varying numbers. No cellular reaction to such areas of necrosis is present to any degree.

Medionecrosis Idiopathica Cystica.—In this condition the media shows foci of basophilic-staining material in which the muscle and the elastic fibers have disappeared. There is no cellular reaction to such areas of necrosis. In certain instances, probably as a later stage of the lesion, cysts filled with mucinous-like material are found.

Aortitis of Undertermined Origin.—Certain cases of mesaortitis have been described from time to time, the causation of which has been entirely obscure. The conditions in these cases do not fit into any of the types just described.[5] Dr. T. B. Mallory, of the Massachusetts General Hospital, recently gave us the opportunity to study 2 striking examples of aortitis of this class. In both cases the patients were young, with no history or clinical or serologic evidence of syphilis.

Histologic examination revealed the following: The intima was thickened because of an increased amount of connective tissue, which in places was rather myxomatous in character. In this thickened intima thin walled vascular channels occurred. The media was greatly scarred and distorted. In some areas the normal elements of the media had

5. Sproul, E. E., and Hawthorne, J. J.: Chronic Diffuse Mesaortitis: Report of Two Cases of Unusual Type, Am. J. Path. **13**:311-323, 1937.

entirely disappeared, being replaced by cellular, vascular connective tissue which was infiltrated by lymphocytes, plasma cells and macrophages. Some foci of necrosis were present, and calcification of necrotic material had taken place in several areas. The adventitia showed marked thickening with dense, rather hyaline collagen, which contained scattered lymphocytes and plasma cells. Several adventitial vessels showed slight to moderate degrees of intimal proliferation. It is obvious that the histologic structure of this aortitis differs essentially from that of gummatous aortitis.

COMMENT

Prior to the identification of Spirochaeta pallida as the causative agent of syphilis, cardiovascular manifestations of the disease were not thought to be common. The reason for this is that the "gumma" was considered the essential lesion of late syphilis, and when it was absent the diagnosis of syphilis was uncertain. The diagnosis of gumma of the aorta was rarely made prior to 1903. The lesion is not discussed in some of the standard textbooks; in others there are contradictory statements as to the frequency of occurrence. Kaufmann,[6] Aschoff,[7] Bell[8] and other pathologists referred to gumma of the aorta without giving statistical evidence. Some pathologists spoke of "miliary gumma" of the aorta, and one is led to believe that this represents an early stage in the development of the usual picture of aortitis.[9] Such was the belief expressed by Martland,[10] who stated:

> Acquired syphilis is essentially a supravalvular sclerosis which may manifest itself in one of several ways. . . . We speak of the process as a sclerosis because the lesion found at autopsy is a deforming defect which has been following previous gummatous infiltrations.

He stated further:

> The process in syphilis never heals completely. In some cases the lesion may remain distinctly gummatous and the involved area soft.

McMeans[11] spoke of "gummatous necrosis" of the medial coat as a common finding, although he did not mention its frequency, nor did he

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6. Kaufmann, E.: Lehrbuch der speciellen pathologischen Anatomie für Studierende und Ärzte, ed. 9 and 10, Berlin, Walter de Gruyter & Co., 1931, vol. 1, pp. 114-115.

7. Aschoff, L.: Pathologische Anatomie, ed. 7, Jena, Gustav Fischer, 1928, vol. 2, pp. 79 and 80.

8. Bell, E. T.: A Text-Book of Pathology, ed. 4, Philadelphia, Lea & Febiger, 1941, p. 206.

9. Von Glahn, W. C.: Cardiovascular Syphilis: Pathology, in Nelson Loose Leaf Medicine, New York, Thomas Nelson & Sons, 1932, vol. 4, p. 341.

10. Martland, H. S.: Syphilis of the Aorta and Heart, Am. Heart J. **6**:1-29, 1930.

11. McMeans, J. W.: The Localization of the Luetic Virus in the Aorta, Am. Heart J. **6**:42-55, 1930.

describe the diagnostic criteria. Peck,[12] in a review of the international literature up to 1927, collected 29 cases of syphilitic involvement of the pulmonary artery, but in only 12, including 1 reported by the author, can the diagnosis be considered as absolutely certain. In 3 cases there were gummatous lesions, and in 2 cases there also were gummas of the aorta. He pointed out that syphilis of the aorta is manifested in two ways, one of which is the gumma, and stressed that "the macroscopic gumma is its characteristic form." In speaking of the cellular infiltration around the nutrient vessels in the adventitia and newly formed channels in the outer portion of the media, Warthin[13] stated that these infiltrations are often large enough to be regarded as miliary gummas, but the development of well defined gummatous nodules with caseating centers and giant cells is rare. When they do occur, they are usually multiple.

In a study of 126 cases of syphilitic aortitis Clawson and Bell[14] encountered 3 cases of gumma of the heart, but no mention was made of an aortic gumma. Winternitz,[15] Wright-Smith,[16] Renner[17] and Šikl[18] each reported a case in which there was postmortem evidence of gummatous aortitis. It is of interest that an examination of the cases of gummatous myocarditis reported in the literature indicates that gummatous aortitis was absent. Contrariwise, in the cases of gummatous aortitis studied by us and reported in the literature, gummatous myocarditis did not coexist.

Thus both our experience and a study of the literature indicate that true macroscopic gummatous aortitis, such as occurred in the 3 cases reported here, is rare. Although such a condition is referred to in textbooks on pathology,[18] a study of detailed reports indicates that the total number of adequately described cases reported in the literature, including the 3 described here, does not exceed 10. The condition, however, must be more common than indicated by the literature. Miliary

12. Peck, S. M.: Pathologic Anatomy of Syphilis of the Pulmonary Artery: Report of Case and Review of Literature, Arch. Path. **4**:365-379 (Sept.) 1927.

13. Warthin, A. S.: The New Pathology of Syphilis, Am. J. Syph. **2**:425-452, 1918.

14. Clawson, B. J., and Bell, E. T.: Heart in Syphilitic Aortitis, Arch. Path. **4**:922-936 (Dec.) 1927.

15. Winternitz, M. C.: The Pathology of Syphilitic Aortitis with a Contribution to the Formation of Aneurysms, Bull. Johns Hopkins Hosp. **24**:212-216, 1913.

16. Wright-Smith, R. J.: Gummata of the Aorta with Rupture into the Pericardium, J. Path. & Bact. **31**:585-586, 1928.

17. Renner, C.: Gummöse Aortenentzündung infolge erworbener Syphilis beim Jugendlichen (Arteriitis gummosa), Ztschr. f. Kreislaufforsch. **26**:807, 1934.

18. Šikl, H.: Ungewöhnliche Ursache des plötzlichen Todes bei Aortenlues: frisches Gumma mit positivem Spirochätenbefund an der Abgangsstelle der linken Kranzschlagader, Centralbl. f. allg. Path. u. path. Anat. **57**:228-232. 1933.

gumma found on microscopic examination of the aorta, on the other hand, occurs more frequently. In our series it was encountered once in 45 cases of chronic syphilitic aortitis, and, as we indicate, this ratio is minimal. Whether in all cases of chronic syphilitic aortitis the lesions go through the microscopic gummatous stage at one time in their development cannot be stated.

The symptomatology of macroscopic or microscopic gummatous aortitis is not specific. Lesions of the wall of the arch of the aorta without perforation, aneurysmal dilatation or involvement of the coronary arteries or the aortic valve is not responsible for symptoms. If gummatous lesions, on the other hand, occlude the coronary arteries, such symptoms as pain, dyspnea, cardiac asthma or pulmonary edema can develop.

The diagnosis of gummatous aortitis can be suspected only in rare instances in young persons without aortic insufficiency but with a history of syphilitic infection in whom thoracic pain and rapidly progressing heart failure are associated with attacks of cardiac asthma and pulmonary edema. At times gumma of the aorta occluding the coronary arteries can be responsible for sudden death. This happened in the case reported by Šikl.[18] Occlusion of the coronary arteries by gumma of the aorta occurred also in the case reported by Renner [17] and in case 1 in our series.

It is of interest that in 2 of the 3 cases of macroscopic gummatous aortitis reported by us rheumatic lesions of the heart coexisted. Similarly in the case reported by Renner [17] rheumatic heart disease coexisted with gummatous aortitis. Sohval [19] reported 2 cases of gumma of the myocardium. In 1 of these cases both rheumatic and syphilitic lesions were present. One wonders whether the existence of these rheumatic lesions is a mere coincidence. The question is raised as to whether rheumatic fever, which is prone to produce an acute cellular hyperergic reaction in the myocardium or in the root of the aorta, enhances the tendency to the development of gummas, particularly in patients who have received but partial antisyphilitic treatment. The latter was the situation in cases 1 and 2 in our group. The significance of the combination of syphilitic and rheumatic heart disease has been discussed by several writers, including Lisa and Chandlee [20] and Swanson.[21]

Case 3 was unusual insofar as there were large syphilitic gummatous lesions located between the aorta and the pulmonary artery. These lesions were responsible for the perforation of the aorta into the trachea.

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19. Sohval, A. R.: Gumma of the Heart: Report of Two Cases, Arch. Path. **20**:429-444 (Sept.) 1935.

20. Lisa, J. R., and Chandlee, G. J.: The Heart and Great Vessels in Combined Syphilitic and Rheumatic Infection, Arch. Int. Med. **54**:952-980 (Dec.) 1934.

21. Swanson, H.: Combined Syphilitic Aortitis and Rheumatic Disease of the Heart: Report of Four Cases, Am. Heart J. **18**:672-683, 1939.

This is the only case with which we are familiar in which gummatous aortitis was associated with a small aneurysm of the aorta. In 1927 Peck [12] was able to collect from the literature but 2 cases of similar occurrence in which gumma of the aorta and of the pulmonary artery coexisted.

SUMMARY

Three cases of macroscopic gummatous aortitis are reported. In case 1 the gummatous process of the aorta completely occluded the right coronary artery and partially occluded the left one. In case 2 gummatous lesions were present also at the base of the aortic valve. In case 3 an extensive gummatous process affected not only the aorta but the pulmonary artery; the necrotic gummatous lesions resulted in perforation of the aorta into the trachea. In none of these 3 cases was there gumma in the myocardium.

Gummatous aortitis is mainly localized in the media, but usually the adventitia and the intima are also affected. Macroscopic gummatous aortitis is rare, and the number of authentic cases described in the recent literature, including the 3 described by us, totals less than 10. In addition to the case reported here of occlusion of the coronary arteries by gumma, only 2 cases of this condition were found in the literature.

Gummatous lesions of the aorta are responsible for symptoms only if they lead to narrowing or occlusion of the coronary arteries or to perforation of the aorta. Dyspnea, orthopnea, precordial distress, cardiac asthma, pulmonary edema and hemoptysis, when present, are referable to such lesions of the coronary arteries or the aorta.

Of 360 cases of chronic syphilitic aortitis, microscopic gummas occurred in 8 (1:45). This ratio must be considered minimal. Whether in all cases of chronic aortitis the lesions go through a stage of microscopic gummatous aortitis is not known.

In 3 of the 360 cases of chronic syphilitic aortitis an acute abscess-like lesion was encountered. In a control group of 224 cases similar "acute aortitis" occurred in 6 cases (in 1 associated with mediastinitis, in 1 with lymphatic leukemia and in 4 with medionecrosis idiopathica cystica). Chronic lesions of the aorta predispose to secondary acute abscess-like lesions.

The differential morphologic characteristics of gummatous aortitis, on the one hand, and those of acute bacterial aortitis, rheumatic aortitis, tuberculosis of the aorta, atherosclerotic necrosis, medionecrosis idiopathica cystica and aortitis of undetermined origin, on the other hand, are described.

In the group of 360 cases of chronic syphilitic aortitis, atheromatous changes over the area affected by the syphilitic lesions were prominent. This suggests that chronic syphilitic lesions of the aorta predispose to the development of local atherosclerosis.

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CONGO RED TEST FOR AMYLOID DISEASE

A QUANTITATIVE TECHNIC

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Prior to the demonstration by Bennhold [1] that a diagnosis of amyloid disease could be based on the selective affinity of deposits of this substance within the body, any decision as to the presence of amyloid deposits in the body rested on presumptive data. In another article we [2] have presented cases that we have encountered in which this test was of service in arriving at a diagnosis. Even our restricted data demonstrate the utility of this little known test. Bennhold's original technic of the injection of 10 cc. of a 1 per cent congo red solution has been used since his method first appeared.[3] While our work was in progress Friedman and Auerbach [4] and later Taran [5] eliminated the factor of possible hemolysis by precipitating proteins with alcohol and (according to Taran) with acetone.

METHOD

Technic.—We have made several modifications and refinements in the technic of performing this test, which yields information concerning the rate of removal of congo red from the blood stream. In place of using a stated amount of the dye for each patient, we have selected a dose graded according to the patient's weight: 4 mg. per kilogram of body weight.

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1. Bennhold, cited by Harmon and Kernwein.[2]

2. Harmon, P. H., and Kernwein, G.: Utility of the Congo Red Test in Diagnosis and in Differential Diagnosis, Arch. Int. Med., this issue, p. 421.

3. Bookman, A., and Rosenthal, J., cited by Harmon and Kernwein.[2] Barker, N. W., and Snell, A. N., cited by Harmon and Kernwein.[2] Shapiro, P. F., and others, cited by Harmon and Kernwein.[2] Rosenblatt, M.: Amyloidosis and Amyloid Nephrosis, Am. J. M. Sc. **186**:558, 1933; The Clinical Manifestations of Amyloidosis, Ann. Int. Med. **8**:678, 1934.

4. Friedman, M. M., and Auerbach, O.: An Improved Congo Red Test for Amyloidosis, J. Lab. & Clin. Med. **21**:93, 1935.

5. Taran, A., cited by Lipstein, S., and Auerbach, O.: An Evaluation of the Congo Red Test for Amyloidosis, Quart. Bull., Sea View Hosp. **2**:120, 1937.

Four minutes and one hour after injection of this quantity of dye samples of blood are regularly removed for examination. If the presence of amyloid disease is suspected, intermediate specimens should be obtained. When the quantity of amyloid is large, as indicated by the presence of a palpable spleen and/or liver, we obtain samples of blood nine and fourteen minutes after injection. Not infrequently under these circumstances one or both of the specimens show only a trace of the dye remaining. Just prior to injection of the dye 10 cc. of blood is drawn, as a source of plasma for preparation of the usual standards, as described later. Any hemolysis is detected in this control, and if it occurs the whole test is repeated. To prevent coagulation 1.4 per cent sodium oxalate solution in distilled water is mixed with the blood withdrawn in the proportion of 1 volume of oxalate solution to 4 volumes of blood. Five cubic centimeters of oxalated blood (1 cc. of oxalate solution and 4 cc. of blood) is the usual sample. The specimen of blood is then centrifuged, and the oxalated plasma is drawn off the underlying corpuscles.

Standards.—These are made from an aqueous stock solution of 0.05 per cent congo red. Two cubic centimeters of oxalated plasma prepared prior to injection of the dye is placed in each of two 10 cc. volumetric flasks. There are then added varied quantities of the stock congo red solution, usually 0.3 and 0.2 cc. These standards, when diluted with distilled water to the mark on the flask, contain, respectively, 15 and 10 micrograms of congo red per cubic centimeter, calculated on the basis of the oxalated plasma prior to dilution. If amyloid disease is indicated by the test, even the specimen of blood drawn four minutes after injection will contain a reduced concentration of the dye, as compared with a similar specimen from a normal person, so that standard solutions for comparison are then prepared with 0.1 and 0.05 cc. of the dye in 2.0 cc. of oxalated, uncolored plasma, each mixture being diluted with distilled water in a 10 cc. volumetric flask, as previously described. These standards contain, respectively, 1.5 and 2.5 micrograms of congo red per cubic centimeter.

Calculations.—The various specimens of blood are then compared with the appropriate standards by means of the colorimeter. The concentration of congo red in each specimen of original blood plasma can then be calculated by the following formula, in which S = micrograms per cubic centimeter of congo red in the diluted standard: $S \times 1.25 \times 5 =$ the concentration in micrograms per cubic centimeter of congo red in the original circulating blood. The percentage of dye left in the blood stream after one hour as compared with that present after four minutes can also be readily calculated. Check comparisons have shown that the maximum error is about 10 per cent, the average error being between 5 and 8 per cent, when oxalated blood is compared with standards prepared as described. The test is preferably done in the morning prior to the ingestion of the first meal of the day, so that alimentary lipemia will not be a disturbing factor in the colorimetric comparisons. If this is not possible, the test can be made five or six hours after the last previous meal. A sample of blood taken promptly after the ingestion of a meal cannot be accurately compared with one taken an hour later. In about one fourth of the patients having amyloidosis that we have encountered there is a slight shift toward an orange color in the specimens withdrawn after the dye has been in the blood stream, which renders the unknown samples not quite so suitable for comparison to the standards. Although error is introduced under such circumstances, the additional amount is not great. That this phenomenon is not due to blood hemolyzed during centrifugalization is controlled by the color of the sample of plasma obtained prior to dye injection.

When one has determined that the dye has all disappeared from the circulating blood stream in less than one hour and that appreciable amounts of amyloid are present, determination of the disappearance time of the dye on different dates after the intravenous injection of the standard dose of 4 mg. per kilogram may give a

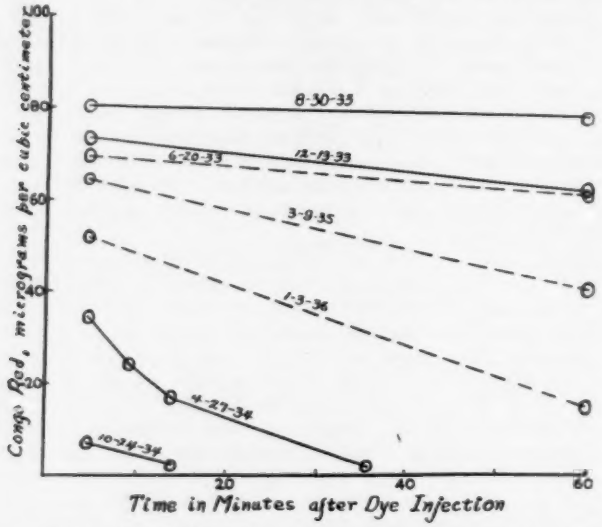

Fig. 1.—Acceleration in the rate of clearance of congo red from the blood stream with the accumulation of amyloid in 2 patients. The curves for each are designated by broken and by unbroken lines, respectively.

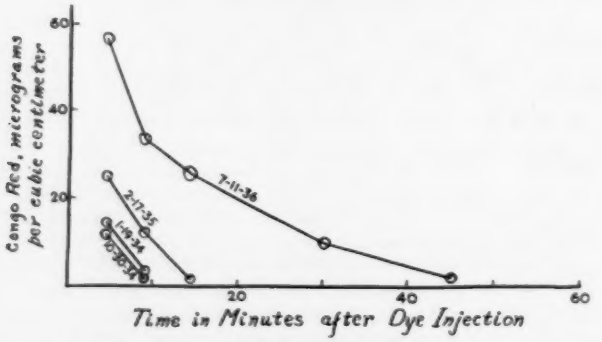

Fig. 2.—Deceleration in the rate of clearance of congo red from the blood stream with the disappearance of amyloid in 1 patient.

rough estimate as to whether the amount of amyloid present is increasing or decreasing (figs. 1 and 2). Determination of the disappearance time is done in the same way that quantitative determination of the total quantity of dye in oxalated blood

plasma is made except that withdrawal of specimens of blood is done every five minutes after the initial four minute specimen is obtained for a total of four specimens exclusive of the initial specimen. The time corresponding to the specimen

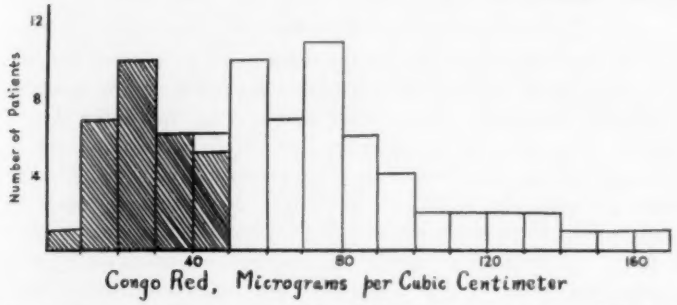

Fig. 3.—Concentration of congo red in the blood of persons with amyloid disease (shaded areas, twenty-nine determinations) and normal controls (unshaded areas, fifty determinations) four minutes after intravenous injection of the dye.

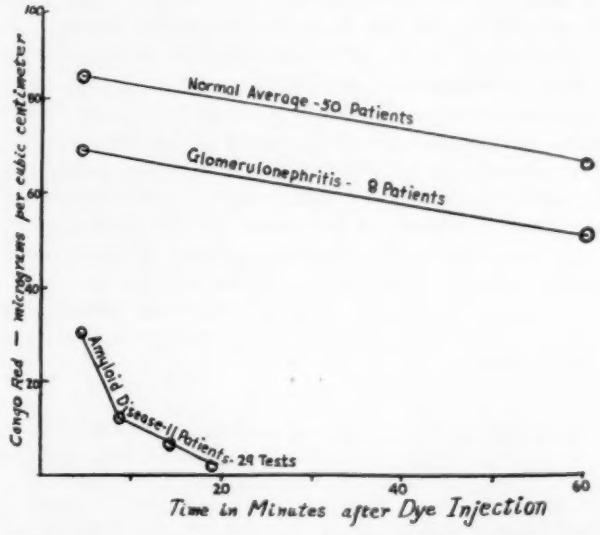

Fig. 4.—Average rate of disappearance of congo red from the blood stream in normal persons and in patients with glomerulonephritis and with amyloid disease.

in which the concentration of dye is so small that it cannot be estimated colorimetrically is designated as the time of disappearance.

Estimation of the dye in the urine is much less accurate than its estimation in blood plasma, as it is not possible to set up standards in urine that are comparable with the excreted product containing the dye. Production of a blue

color by acidification has not been any further aid. With care in handling the specimens of blood during collection and centrifugalization, we have not found it necessary to precipitate the proteins by alcohol or acetone, as advocated by Friedman and Auerbach and by Taran.

RESULTS

This report is a summary of the results of one hundred and thirty-nine tests, 92 of which were performed according to the quantitative technic just described. The average level of congo red in the blood four minutes after intravenous injection was 85.7 micrograms per cubic centimeter in fifty determinations made on normal controls, 29.6 micrograms per cubic centimeter in twenty-nine determinations made on 11 patients with amyloid disease and 71.5 micrograms per cubic centimeter in eight determinations made on patients suffering from chronic glomerulonephritis. Figure 1 demonstrates the accumulation of appreciable stores of amyloid during the progression of the disease. Conversely (fig. 2), similar curves also will demonstrate deceleration of removal from the blood stream, a phenomenon which presumably parallels recovery and disappearance of amyloid deposits. This phenomenon has been discussed more freely in another paper,[2] dealing with the clinical phases and the diagnosis of amyloid disease. Figure 3 presents a graphic analysis of the initial levels of congo red attained in the blood in seventy-nine determinations on the normal persons and those with amyloidosis. The lower levels and the faster disappearance in persons with amyloid disease is related to the immediate absorption of the dye from the blood stream by deposits of this substance.

The average disappearance curves of the dye from the blood stream in three classes of patients as determined by our tests is given in figure 4. The average rate of disappearance in persons having amyloid disease is radically different from that in normal controls and from that in persons suffering from albuminuria due to chronic glomerulonephritis. The interpretation, utility and reliability of this test have been discussed in another paper.[2]

SUMMARY

A quantitative technic for execution of the congo red test is described. Standards are given, and average disappearance curves and values for the level of congo red in the blood are presented.

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UTILITY OF THE CONGO RED TEST IN DIAGNOSIS AND IN DIFFERENTIAL DIAGNOSIS

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During the past few years the congo red test for the confirmation of amyloid deposits in the body has been serviceable in our hands in elucidating the nature of obscure enlargements of the spleen and the liver. Since this test is not as well known as it deserves to be, and since we feel that many problems in diagnosis might be clarified by its use, reports are presented of 7 cases in which this test was of great value in arriving at a diagnosis. It should be emphasized that if positive, the information derived from the test is unequivocal, but there may be a small to moderate degree of amyloid present, undetectable by the test.

Bennhold [1] found that congo red, if carefully prepared, could be injected intravenously without danger. He presented 10 cases demonstrating that amyloid deposits in the liver would remove the dye rapidly from the circulating blood. This author also observed that patients with albuminuria due to noninflammatory disease of the kidney (nephrosis) eliminated quantities of the dye in the urine. There have been but a few additional reports [2] on the application of the method to a series of patients since the appearance of the original communication.

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1. Bennhold, H.: Ueber die Beziehungen des Kongorotes zur amyloiden Substanz und über den Mechanismus der beschleunigten Farbstoffausscheidung bei tubulären Nierenkrankheiten, Klin. Wchnschr. **3**:1711, 1924; Ueber die Ausscheidung intravenös einverleibten Kongorotes bei den verscheidensten Erkrankungen insbesondere bei Amyloidosis, Deutsches Arch. f. klin. Med. **142**:32, 1923.

2. (*a*) Bookman, A., and Rosenthal, J.: The Clinical Value of Intravenous Injection of Congo Red in the Diagnosis of Amyloid Disease, Am. J. M. Sc. **173**: 396, 1927. (*b*) Barker, N. W., and Snell, A. N.: The Congo Red Test with Special Reference to Excretion of the Dye in the Urine, J. Lab. & Clin. Med. **16**:262, 1930. (*c*) Shapiro, P. F.: Lipoid Nephrosis: Pathology, Genesis and Relation to Amyloidosis, Arch. Int. Med. **46**:137 (July) 1930. (*d*) Wallace, J.: Diagnosis of Amyloid Disease by the Intravenous Injection of Congo Red, Lancet **1**:391, 1932. (*e*) Rosenblatt, M.: The Clinical Manifestations of Amyloidosis, Ann. Int. Med. **8**:678, 1934; (*f*) Amyloidosis and Amyloid Nephrosis, Am. J. M. Sc. **186**:558, 1933. (*g*) Lipstein, S., and Auerbach, O.: An Evaluation of the Congo Red Test for Amyloidosis, Quart. Bull., Sea View Hosp. **2**:120, 1937.

Elsewhere [3] data from a series of tests have been analyzed. All previous authors have employed the original method of Bennhold, which consists merely of a comparison of the amount of the dye left in the blood stream at the end of one hour with that originally present just after injection.

METHOD

Bennhold injected either 10 cc. of a 1 per cent aqueous solution of congo red or 15 cc. of a 0.75 per cent solution intravenously. Four and sixty minutes after injection samples of blood were drawn, coagulation being prevented by coating tubes with paraffin. The two samples were then compared colorimetrically, and the percentage of dye left after sixty minutes was expressed in terms of the four minute specimen, which was used as a standard.

We have modified the test by injecting intravenously 4 mg. of congo red per kilogram of body weight as a 1 per cent solution. Specimens of blood are removed four and sixty minutes after injection. When the presence of amyloid disease is suspected and we wish to estimate roughly the amount of amyloid present, intermediate specimens are obtained.[3] For example, in the presence of a large quantity of amyloid, specimens drawn ten to fifteen minutes after injection of the dye usually do not show any trace of red or pink coloration. It is then desirable to repeat the test and determine the disappearance time of the dye from the peripheral blood stream. A detailed description of the technic can be found in another report.[3] The amount of the dye in micrograms per cubic centimeter of original blood plasma is obtained.

RESULTS

We have made one hundred and thirty-nine injections of congo red according to the technic just described in 69 different patients. Extreme and median values for the amount of congo red present in the circulating blood stream (oxalated plasma) after the intravenous injection of the standard amount are given in table 1. In accordance with the experiences of Bennhold [1] and others,[2] whenever a palpably enlarged spleen or liver has been produced by amyloid infiltration of that organ, the intravenous injection of congo red is followed by a rapid disappearance of the dye from the peripheral blood stream, thus leaving colorless the specimen of blood drawn after an hour. The interpretation of a partial clearance of the dye from the blood stream after an hour will be discussed later. We have preferred to make a clinical and laboratory diagnosis of amyloid disease only when the dye was completely removed from the blood after an hour; however, we have included as an illustration of a positive test a single case (8) in which there was 72.7 per cent absorption in an hour, since subsequent autopsy disclosed the presence of amyloid. Lipstein and Auerbach [2g] investigated this question, having available 12 cases in which there was greater than 50 per cent absorption of the dye during life but in which there was no demon-

3. Harmon, P. H., and Kernwein, G.: Congo Red Test for Amyloid Disease: A Quantitative Technic, Arch. Int. Med., this issue, p. 416.

strable amyloid at necropsy. In only 1 of these cases was there complete absorption of the dye in one hour. Thus, if complete absorption is adopted as the standard of a "positive" test, rather than absorption of more than 50 per cent, as advocated by Bennhold, a positive congo red test will have great significance. In all (8) of our patients in whom complete clearance of the dye from the blood stream occurred in one hour and who subsequently came to autopsy amyloid was encountered in the organs in large quantities. The presence of amyloid in the liver, spleen and other organs was confirmed at necropsy in 10 of our patients. The test indicated large quantities of amyloid in 8 additional patients. Of this last-named group, 2 had a palpably enlarged liver at the time of the first examination and 2 appeared to be recovering from amyloid disease as judged from the results of the dye test, disappearance of albuminuria and anemia and improvement in general well-being. The

TABLE 1.—*Concentration of Congo Red After Intravenous Injection of Four Milligrams per Kilogram of Body Weight, Calculated as the Amount in Undiluted Blood Plasma (Micrograms per Cubic Centimeter)*

Clinical Status	No. of Patients	4 Min. After Injection			1 Hr. After Injection		
		Lowest	Highest	Median	Lowest	Highest	Median
History of chronic suppuration; no amyloid disease	38	49.1	128.3	75.0	24.4	106.5	55.0
Amyloid disease	11*	4.7	57.3	26.4	0	14.3	0
Acute and/or chronic glomerulonephritis	8	50.8	106.3	67.5	21.8	90.6	48.1

* Twenty-nine tests on 11 patients.

remaining patients had appreciable amounts of amyloid deposits as judged by the dye test, but their livers and spleens were not palpable. In other instances the congo red test has enabled us either to dismiss the possibility of amyloid disease or to demonstrate the nature of an obscure enlargement of the liver or the spleen.

REPORT OF NINE CASES IN WHICH THE TEST WAS OF VALUE IN DIFFERENTIAL DIAGNOSIS

CASE 1.—A boy 9 years of age with a history of two years' disability from generalized juvenile atrophic arthritis (Still's disease) was first tested in April 1932. During fifteen months previously there had occurred four periods of several weeks when activity of many joints was present, with a daily exacerbation of temperature to 102.4 or 104 F. (39 or 40 C.). He had been treated by conservative orthopedic procedures aimed at prevention of deformity. Many repeated blood cultures remained sterile. During the early months of 1932 there appeared progressive enlargement of the liver, so that when we first saw the patient the liver was palpable 6 cm. below the right costal margin in the midclavicular line. Flaring costal margin and a protuberant abdomen were present. The patient was moderately anemic, the hemoglobin concentration (Sahli) being 60 per cent and the red

blood cells numbering 3,090,000 per cubic millimeter. The patient was excreting a large quantity of albumin in the urine, graded by the Heller nitric acid test as 4 plus. Only an occasional epithelial cast was found in the urine. No suppuration had been present at any time. Fifteen minutes after injection of 4 mg. per kilogram of congo red intravenously the dye all disappeared from the blood stream. None appeared in the urine. The diagnosis was amyloid disease involving the liver and kidneys, occurring as a complication of generalized juvenile atrophic arthritis (Still's disease).

CASE 2.—A boy aged 12 had a fifteen months' history of multiple chronic osteomyelitis involving the mandible, the left and the right femur, the left fourth metacarpal, the right tibia, the right scapula, the right fifth rib and the right humerus, with a pathologic fracture of the right femur. Liver dulness was increased to the right costal margin, but that organ was not palpable. The patient had severe secondary anemia, with a hemoglobin concentration of 45 per cent (Sahli) and a red cell count of 2,900,000 per cubic millimeter. There was no albuminuria. Four milligrams per kilogram of congo red was injected intravenously. The specimen of blood removed at the end of one hour showed the same amount of dye as that present four minutes after injection. Thus, regardless of the long history of severe and widespread suppuration and the severe anemia, the congo red test showed no amyloid to be present at this time. During the following nine months, ostectomies were done and two large soft tissue abscesses were drained. During a period of six weeks, the patient ran a low grade fever (temperatures of 99.5 to 100.5 F. [37.5 to 38 C.]) and a moderate amount of albumin appeared in the urine. The liver and the spleen were still not palpable. A repetition of the congo red test at this time demonstrated a total disappearance of the dye from the blood stream in twenty-five minutes. None appeared in the urine. Later tests showed a still more rapid disappearance of the dye from the blood stream. This patient was thus shown to have acquired amyloid disease of moderate severity while under hospital treatment for multiple chronic osteomyelitis. He subsequently died and was examined at necropsy.

CASE 3.—A 12 year old boy had had chronic osteomyelitis of the lower portion of the left tibia for fifteen months. The lesion had been healed for twelve months when a blow to the area was followed by an acute local recurrence of the infection. In addition to the local condition, we observed that the patient's urine contained much albumin and 20 to 30 red cells and 5 to 10 white cells per high power field of the microscope. These urinary changes had also been present on the patient's first admission but had rapidly subsided as the infection was brought under control. Examination of the blood showed that the patient was not anemic. At neither time was the liver or the spleen palpable. The congo red test, performed by the intravenous injection of 4 mg. per kilogram of the dye, showed that 71.8 micrograms per cubic centimeter (74 per cent of 86.3 micrograms per cubic centimeter, the amount present after four minutes) remained in the blood after one hour. None of the dye was excreted in the urine. Nine months after the first test the patient returned with another local recurrence of osteomyelitis, with similar urinary findings. The dye test was repeated, with similar results. The diagnosis was chronic glomerulonephritis and recurrent osteomyelitis.

CASE 4.—A man aged 50 had had a chronic cough following pneumonia for six years. During the six months just before we saw him the cough had been more productive and the sputum purulent. The patient had been weak, and there had been a loss in weight of 30 pounds (14 Kg.) during the previous year.

The physical examination showed among other things marked clubbing of fingers. The spleen and the liver were each palpable 6 cm. below the costal margin in the respective anterior axillary lines. There were a few coarse rales over the base of the chest. Examination of the blood showed a hemoglobin concentration of 52 per cent (Sahli) and a red cell count of 3,100,000 per cubic millimeter. The white cells numbered 6,000 per cubic millimeter. The urine showed appreciable albumin, graded from 2 plus to 4 plus, with a moderate number of epithelial casts and occasional white cells and red cells. Roentgenograms of the chest showed some soft disseminated infiltrative lesions in the lower portion of the chest on the right side, interpreted as bronchiectatic markings. The nonprotein nitrogen content of the blood was 118 and 84 mg. per hundred cubic centimeters on two observations, and the index of urea clearance was 5 and 9 (normal 40 to 65) on two different tests. The congo red test (4 mg. per kilogram of body weight) showed 90 per cent retention of the dye in the blood stream after one hour. None appeared in the urine. The final diagnosis was chronic glomerulonephritis with nitrogen retention, chronic bronchiectasis, secondary anemia and cardiac decompensation, with chronic passive congestion of the liver, spleen and kidneys.

CASE 5.—The patient was a woman aged 32. Infection had occurred at another hospital after an open operation for bilaterally fractured patellas. This was followed by unilateral pyoarthrosis and almost complete fibrous ankylosis of the same knee. When the patient was seen by Dr. D. B. Phemister, fourteen weeks after the infection had occurred, there was still a draining sinus present and some swelling and tenderness about the knee, with only 5 degrees or less of passive motion possible. The patient was having a persistent afternoon temperature, ranging between 100.5 and 102 F. (38 to 38.8 C.). The spleen was palpable 3 cm. below the left costal margin in the anterior axillary line. The liver was not palpable. The patient had a moderate degree of secondary anemia, with a hemoglobin concentration of 65 per cent and a red cell count of 3,550,000 per cubic millimeter. The congo red test, done by the injection of 4 mg. per kilogram intravenously, showed 66.9 micrograms of the dye per cubic centimeter to be present in the blood stream at the end of an hour (85 per cent of 75 micrograms per cubic centimeter, the amount present after four minutes). None was excreted in the urine. The dye test indicated that amyloid was not present in this patient at this time.

CASE 6.—A man 65 years of age complained of dysphagia for solid food and of a sensation of a foreign body present in the lower part of the throat for seven weeks prior to seeking medical advice. He had lost 41 pounds (19 Kg.) in weight during the previous four months. On physical examination the patient showed general emaciation and cachexia. Other results of examination were not remarkable except for the enlargement of the liver to a point 10 cm. below the costal margin in the right midclavicular line. The edge of this organ was firm and rounded. A trace of albumin was present in the urine. Red cells numbered 4,070,000 per cubic millimeter. Roentgen examination with the aid of an opaque contrast medium administered by mouth demonstrated a lesion in the upper portion of the esophagus opposite the second to the sixth thoracic vertebra. Biopsy of material obtained through an esophagoscope revealed an epidermoid carcinoma. The congo red test was made by the intravenous injection of 4 mg. per kilogram of body weight. There was 61.3 micrograms of dye per cubic centimeter (82 per cent of 74.4 micrograms per cubic centimeter, the amount present after four minutes) remaining in the patient's blood stream after one hour. None appeared in the urine. The diagnosis prior to operation was carcinomatous stenosis of the esophagus. The cause

of the enlarged liver was not definitely decided, except that it was not due to the deposition of amyloid. At an abdominal exploration, at which time a gastrostomy was also done, a firm and finely nodular liver, typical of alcoholic cirrhosis, was encountered. The patient's immediate postoperative course was excellent, as he was soon able to take fluids and food through the gastrostomy opening. During the course of subsequent high voltage roentgen therapy, the patient lost more weight and strength, an intractable cough developed and the patient finally died. At necropsy amyloid was not present in the enlarged liver.

CASE 7.—A boy 6 years of age presented himself with draining sinuses in the left arm and left leg. He was obviously anemic, underweight and malnourished. The onset had been ushered in with chills and fever following trauma, the patient having been treated for "malaria" before a definite diagnosis was established. Swelling of the scrotum and the abdomen had occurred during the course of the acute illness, and fluid had accumulated in the chest, necessitating aspiration of the chest six times in the four months before the patient was seen at the University of Chicago Clinics. On admission he had edema of the eyelids. On the left side, the superficial veins of the neck were distended and there was a venous pattern on the anterior aspect of the chest. Dulness and diminished breath sounds were present in the chest on the left side. The spleen was palpable 8 cm. below the right costal margin in the left nipple line. The upper portion of the left humerus was palpably enlarged, and three healed scars were present. There were two discharging sinuses over the left tibia. Examination of the blood showed the red cell count to be 5,040,000 per cubic millimeter, the white cell count 10,600 per cubic millimeter and the hemoglobin concentration 80 per cent. Albumin (1 plus) was present in the urine. Roentgenograms showed a massive pleural effusion on the left side, which on aspiration yielded seropurulent fluid. Changes characteristic of chronic osteomyelitis were seen in the left tibia and the left humerus. The congo red test showed 64 micrograms per cubic centimeter in the blood stream at the end of one hour (80 per cent of 80 micrograms, the amount of the blood four minutes after injection). The diagnosis was chronic (left) thoracic empyema and chronic pyogenic osteomyelitis of the left tibia and the left humerus. It was thought that the patient did not have amyloid disease because of the rapid disappearance of the splenic enlargement in conjunction with the negative dye test. His subsequent course proved this to be correct.

CASE 8.—A girl aged 11, a sister of the patient in case 7, presented herself with multiple chronic rheumatoid arthritis (Still's disease) of three years' duration. On entrance and intermittently for the ensuing four years of observation, she presented mild to moderate edema of the face and eyelids, associated with slight to moderate intermittent albuminuria. During three of these four years the patient remained in good general condition, but during the fourth year she began to lose weight, became cachectic and finally died in a coma associated with nitrogen retention. Never at any time was either the liver or the spleen palpable. The congo red test done on two occasions during the first two years of observation showed 88 and 60 per cent retention in the blood stream, but a third test done a few months prior to death showed a blood level of 14.3 micrograms per cubic centimeter at the end of one hour (27.3 per cent of the level of 52.3 micrograms per cubic centimeter four minutes after injection). At necropsy a moderate degree of generalized amyloidosis was found, especially in the kidneys.

CASE 9.—A boy aged 15 years had a tibial leg-lengthening osteotomy performed. For four successive days the color of the lower portion of the leg remained

cyanotic and the temperature elevated. On the fifth and the sixth day definite gangrene of the leg appeared. A pure culture of β hemolytic streptococci was isolated from the wound and from around the pin holes. A midthigh amputation was performed in an attempt to save the patient's life, but he died ten hours after the amputation. Two years before the first surgical procedure it had been observed that he had a trace of albumin in the urine. At that time a congo red test, done because of the history of chronic suppuration, showed that 80 per cent of the dye remained in the blood plasma at the end of an hour. In the ensuing two years the albumin disappeared from the urine. A second congo red test performed the day before death showed 79 per cent of the dye in the blood stream at the end of an hour (initial level after four minutes being 53.4 micrograms per cubic centimeter). The necropsy showed moderate to advanced amyloid infiltration in the glomeruli and slight amyloid infiltration in the liver, spleen and adrenal glands. The septic thrombosis of both renal arteries observed post mortem may have been responsible for the negative dye test on the latter occasion.

DIFFERENTIATION OF NEPHRITIDES BY THE CONGO RED TEST

In Bennhold's report [1] on the use of congo red in the diagnosis of amyloid disease the possibility of utilizing this test to differentiate the types of nephritides was minimized. Since that time, however, there have appeared indications [4] that this dye might be employed in clinical laboratory tests to differentiate chronic glomerulonephritis from nephrosis. The difficulty of segregating certain stages of chronic glomerulonephritis (for example, the nephrotic stage) from pure nephrosis either by clinical appearance or by chemical examination of blood or urine is well known.[5] In an attempt to confirm and clarify the possible utility of the congo red test in this situation the tests summarized in table 2 were carried out. We attempted to correlate the urinary excretion of congo red in 7 patients with various stages and types of chronic nephritis and in 1 patient with orthostatic albuminuria with the amount of protein excreted in the urine during the period of examination. The clinical status of these patients, together with the data compiled in this study, is given in the accompanying table 2. Determinations of the dye were made colorimetrically both in blood plasma and in urine by comparison with standards. The amount found in the urine is an approximation as standards cannot be accurately proposed with urine as a diluent.

It can be seen by reference to table 2 that there was a wide variance between the amount of the dye excreted in the urine after the intra-

4. Nathan, M.: Ueber die klinische Diagnose des Amyloidose mittels Kongorotinjectionen, München. med. Wchnschr. **75**:1883, 1928. Strasser, U.: Die Kongorotprobe auf Amyloid bei nephrotischen Symptomencomplex, Med. Klin. **25**:468, 1929. Shapiro.[2e]

5. Leiter, L.: Nephrosis, Medicine **10**:135, 1931. McClure, W. B.; de Takáts, C. B., and Hinman, W. F.: Mechanism of Edema of the Renal Type, Arch. Int. Med. **51**:819 (June) 1933.

TABLE 2.—*Relation of Proteinuria to Urinary Excretion of Congo Red*

Patient Number	Age of Patient, Years	Diagnosis	Clinical Edema	Total Plasma Proteins, Gm./100 Cc.	Hemoglobin, per Cent (Sahli)	Index of Urea Clearance, (Normal 40=65)	Congo Red		Urinary Excretion	
							Amount in Blood After 1 Hour in Micrograms 1 Cc.	Total Amount Excreted in Urine in 1 Hour, Micrograms	Cc. in 1 Hour	Total Protein in Sample, Gm.
10	28	Acute glomerulonephritis (recovery stage)	0	6.4	80	37	51.2 (66%)	Trace	90	0.518
11	56	Chronic glomerulonephritis	+	3.9	58	27	50.0 (80%)	1,520	65	1.491
12	61	Cardiorenal disease; generalized arteriosclerosis	0	7.2	80	10	90.6 (84%)	662	53	2.534
13	16	Acute glomerulonephritis (nephrotic stage)	+	3.6	70	56	21.9 (34%)	0	80	1.964
14	54	Chronic glomerulonephritis, with acute exacerbation; hypertensive cardiorenal disease	0	6.1	70	5	48.1 (69%)	Trace	87	0.897
15	14	Chronic glomerulonephritis (nephrotic stage)	+	4.7	85	Phenolsulfonphthalein excretion, 60% in 2 hours	24.4 (45%)	950	35	0.221
16	32	Chronic glomerulonephritis	0	5.5	60	6	45.7 (68%)	400	40	0.548
17	19	Orthostatic albuminuria	0	.....	95	....	31.3 (72%)	Trace	47	0.019

venous injection of a standard dose of congo red (4 mg. per kilogram of body weight) and the quantity of protein excreted in the urine during the same period. Further, there was no relation between the level of protein in the circulating blood, the presence of edema clinically, the functional efficiency of the kidney as measured by the index of urea clearance and either the amount of protein in the urine or the amount of congo red excreted in the urine. Normally, in human beings in the absence both of albuminuria and of amyloid deposits in the body, no congo red or a bare trace is excreted in the urine.[6]

COMMENT

The cases presented in this paper demonstrate the value of the congo red test in confirming the clinical impression of amyloid disease and for further clarification of the nature of obscure enlargements of the liver and the spleen. If a positive result, by which we mean complete removal of a standard dose of 4 mg. per kilogram of dye given intravenously, is obtained, there is little likelihood that the condition is other than amyloid disease. Only 1 case (reported by Lipstein and Auerbach) of a "false positive" test is on record if the criterion just mentioned is accepted. There was no explanation given for this singular result. In all of our severely ill patients, in whom complete absorption of the dye was present and who came to necropsy, the presence of amyloid deposits was demonstrable.

When the patients demonstrating only partial absorption of the dye are considered, especially that group in whom 50 to 90 per cent of the dye was removed from the blood stream, there is opportunity for misinterpretation of the result. The criterion originally established by Bennhold for a "positive" test needs modification and more liberal interpretation. It is our opinion that a partial absorption result should be considered as only "suggestive" of the presence of amyloid. Eleven cases were reported by Lipstein and Auerbach in which autopsies failed to yield evidence of amyloid deposits but in which during life more than 50 per cent absorption of the dye has been demonstrated. The tests in 3 of our patients fell into this category. One patient, with Still's disease and 72 per cent absorption, subsequently died, and changes typical of amyloid disease were encountered at necropsy. The other 2 patients are still well, with 51 and 60 per cent disappearance of dye. One of the patients is without any of the suggestive signs of amyloid disease except slight anemia (70 per cent hemoglobin) and intermittent slight albuminuria; in the other an accelerated and typical dye absorption curve later developed, but the patient recovered completely, with reversal of the dye absorption test.

6. Bennhold.[1] Footnote 2.

False negative results may occur and should be interpreted with some caution, especially when other signs point to amyloid disease. In our series 1 patient had a negative test, interpreted according to the first-mentioned criterion (less than 50 per cent absorption). An autopsy was subsequently done, with the finding of amyloid in the organs. Lipstein and Auerbach also reported that in 1 patient in whom changes typical of amyloid disease were observed at autopsy only 35 per cent of the dye was absorbed. In our patient just mentioned thrombosis of the renal arteries was encountered at autopsy, and since the majority of the amyloid was in the kidney, that condition might have accounted for the false negative result. We had 1 patient in whom there was incomplete absorption (72 per cent), while Lipstein and Auerbach described 4 patients (3 showed 90 per cent absorption, and 1 had 95 per cent absorption), all having amyloid demonstrable at autopsy.

The question of recovery from typical amyloid disease associated with complete absorption of the dye can be answered in the affirmative. We have had 2 patients in whom complete reversal of the dye test occurred and a third who remained in excellent health and without anemia or albuminuria for five years. The result of the dye test in the third patient remained positive. In our opinion the 6 "recovered cases" reported by Grayzel and Jacobi[7] should be reduced to 2, inasmuch as the other 4 were probably in a period of spontaneous remission, since they still showed appreciable absorption of the dye and albuminuria. The same is true of the cases reported by Whitbeck.[8] Spontaneous remissions are common in this disorder, when for periods of several months the size of the viscera recedes, the patient gains weight, anemia improves and albuminuria disappears, but the congo red test remains positive. The criterion for recovery in the cases reported by Waldenström[9] was absence of amyloid in biopsy specimens obtained by liver puncture.

Our 2 instances of recovery bring the total number of recoveries from this disease reported in the literature to 11. Four instances were reported by Waldenström.[9] Two recoveries were described by Pearlman,[10] in addition to 2 cases in which regression occurred. In these

7. Grayzel, H. G., and Jacobi, M.: Secondary Amyloidosis: Results of Therapy with Desiccated Whole Liver Powder, Ann. Int. Med. **12**:39, 1938.

8. Whitbeck, B. H.: Liver Meal in the Treatment of Amyloidosis, J. Bone & Joint Surg. **14**:85, 1932.

9. Waldenström, H.: On the Formation and Disappearance of Amyloid in Man, Acta chir. Scandinav. **63**:479, 1928; Ueber das Entstehen und Verschwinden des Amyloids beim Menschen, Klin. Wchnschr. **6**:2235, 1927.

10. Pearlman, A. W.: Regression of Amyloidosis, Quart. Bull., Sea View Hosp. **6**:92, 1940.

2 cases the interpretation of the dye test was questionable, as there was incomplete elimination of the dye from the blood stream. Habein,[11] Rosenblatt[12] and Reimann[13] each reported an instance of recovery in which there was complete reversal of the dye test. Prior to the introduction of the congo red test 4 instances of recovery[14] were recorded, but these recoveries, while suggestive, must remain conjectural, as they cannot be confirmed by modern rigid criteria. It is difficult to estimate the percentage of recovery in cases of this disease, as the reports are in the main of single cases. Judging from our series and those of Waldenström, Grayzel and Jacobi and Pearlman, "permanent" recoveries with reversal of the dye test occur in less than 10 per cent of cases, even when suppuration has been minimized. Elimination of suppurative foci appears to be the only reliable basic means of controlling the disease. Since the complication occurs most frequently in persons with cavernous pulmonary tuberculosis, with secondary infection associated with tuberculous joint disease and with chronic multiple pyogenic osteomyelitis, the difficulty results from unsatisfactory treatment of or response to the original disease. Encouraging results in treatment have been reported with desiccated liver meal by Whitbeck and by Grayzel and Jacobi. However, the use of this material must be considered as an adjuvant to elimination or control of suppuration, inasmuch as the results reported by these authors were not uniformly successful. We treated 4 patients with liver meal for almost a year without observing more benefit than regression similar to that occurring under favorable conditions without this treatment. Periods of "spontaneous" regression in the disease must be fairly common, since they occurred one or more times in 10 of our 11 patients. A regression simulates a "recovery" closely but is distinguished from it by the temporary duration of the regressive phase and failure of the congo red test to reverse during the episode.

It should be pointed out that although suppuration is the most common associated or causative condition in the production of amyloid disease, it is not necessary always to have suppuration as a preliminary condition. It is a common complication of Still's disease (2 instances in our series) and of multiple myeloma.[15] The common association of

11. Habein, H. C.: Amyloidosis: Report of a Case in Which the Patient Recovered, Proc. Staff Meet., Mayo Clin. **9**:261, 1934.

12. Rosenblatt, M. B.: Recovery from Generalized Amyloidosis Secondary to Pulmonary Tuberculosis, Arch. Int. Med. **57**:562 (March) 1936.

13. Reimann, H. A.: Recovery from Amyloidosis, J. A. M. A. **104**:1070 (March 30) 1935.

14. Gardner, W., cited by Pearlman.[10] Kretzschmar, P. H., and Westbrook, B. P., cited by Pearlman.[10] Owen, I., cited by Pearlman.[10] Walker, G. F., cited by Pearlman.[10]

15. Rosenblum, A. H., and Kirshbaum, J. D.: Multiple Myelomas with Tumor-Like Amyloidosis, J. A. M. A. **106**:988 (March 21) 1936.

the disorder with suppuration and the relative hopelessness of ultimate prognosis in a patient in whom the diagnosis of amyloid disease has been established, argues strongly in favor of a periodic check-up by means of the congo red test of persons in whom the control of suppuration by the recognized conservative surgical methods has been imperfect. It further suggests the more common employment of amputation and bone resection when conservative surgical means have not sufficed to bring chronic bone suppuration under control. The employment of these more radical measures within a few weeks or months of the establishment of a positive dye test in instances of single uncontrollable suppurative foci would be a life-saving measure. In retrospect, 1 of our patients likely would not have died had we been successful in obtaining permission to perform a hip joint disarticulation two years prior to the date on which it was finally performed.

Serial and periodic examination by the congo red test of persons harboring a suppurative focus yields valuable data on the minimal time required after the onset of suppuration for enough amyloid to develop to give a positive congo red test. The authorities previously cited (Waldenström, Lipstein and Auerbach and Whitbeck) expressed the belief that one to two years are required after the onset of suppuration until "amyloid disease develops." The data on 9 of our patients are sufficient to fix within a span of a few months the accumulation of sufficient amyloid to give a positive dye test. This period from onset of suppuration (or arthritis in 2 patients with Still's disease) was nine months for a 5 year old child, one and a half years for 2 patients, two years for 3 patients, four years for 2 patients and eight years for 1 patient. It is possible that age may be a factor of relative resistance to amyloid disease, but we do not have sufficient data either to prove or to disprove this contention.

CONCLUSIONS

1. The congo red test is valuable as an aid in differential diagnosis of obscure swellings of the liver and the spleen.

2. When the test is positive (rapid disappearance of the dye from the circulating blood plasma within a few minutes), a diagnosis of amyloidosis can be made.

3. The test gives no clue to the distribution of the amyloid deposits in the body.

4. Slight to moderate amounts of amyloid may be present, and the test will fail to reveal this fact (2 illustrative cases are reported). A negative test is not positive proof that amyloid is not present, but when taken in conjunction with other data it may point to that conclusion.

5. The test is of no value in distinguishing between the stages of chronic glomerulonephritis or nephrosis or between these two states

and orthostatic albuminuria, although the dye is excreted in the urine in large quantities when albuminuria is present in the absence of amyloidosis.

6. Methods of determining blood volume using congo red are invalid in the presence of amyloidosis or albuminuria from any cause.

7. The congo red test is valuable in following the course of patients with amyloid disease and is of some prognostic value. In recovery from this disease the positive dye test is the last sign to disappear, this occurring some months after disappearance of palpable organs, anemia and albuminuria.

8. The minimum time for the accumulation of sufficient amyloid to give a positive dye test is nine months, and the average is one and one-half to two years.

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HODGKIN'S DISEASE WITH SPECIFIC LESIONS APPEARING FIRST IN THE SKIN

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PHILADELPHIA

In cases of chronic lymphogranulomatous disease, particularly when the gross or the histologic lesions accessible for examination are not pathognostic of any one recognized entity, both clinical and histologic diagnoses may be confused. This is especially true in cases of Hodgkin's disease when it is unusual in character. In some cases of atypical disease the diagnosis may be made because no other classification is possible in the light of present knowledge, and in others, as in the one reported here, it may be mistaken for other diseases. The final diagnosis is often established at necropsy, when all available data are at hand.

In the present case Hodgkin's disease was suspected early in the course, but because of the unusual onset with the earliest and most prominent lesions in the skin and the absence of demonstrable enlarged lymph nodes and later because of the histologic changes in excised bits of tissue from the skin, lung, spleen and bone marrow, the possibility of chronic, relapsing, febrile, nonsuppurative panniculitis arose. This syndrome, also known as Weber-Christian disease, of which about 20 cases have been recorded, seems to be almost as rare as cases of Hodgkin's disease in which the first specific lesions appear in the skin. It is of unknown causation; occurs mostly in women; is characterized by multiple inflammatory nodules in the panniculus adiposus, which heal with atrophy to leave depressions in the skin, and like Hodgkin's disease, is relapsing in type with prolonged irregular, intermittent fever. In our case the condition conforms with this definition except for the visceral involvement, the occurrence in a man, the occasional ulceration of a cutaneous lesion and the fatal end. So far as the cutaneous lesions are concerned, it was indeed a case of panniculitis but with grave systemic involvement as well, all a part of the chronic granulomatous condition called Hodgkin's disease.

From the Department of Medicine and the Clinical Laboratory, Jefferson Medical College Hospital.

Presented at the meeting of the Association of American Physicians, Atlantic City, N. J., May 6, 1941, as a report of a possible case of relapsing, febrile, nodular panniculitis.

REPORT OF A CASE

In March 1939 R. B., a machinist aged 45, tired more easily than usual. In April several "fiery red" spots which were about 5 mm. in diameter, itched and at times were painful enough to keep him awake at night appeared on the extensor surface of the right arm near the elbow. After several days the spots gradually faded and left pigmented areas. He continued to work but lost weight, strength and appetite. Three weeks later, similar but more numerous and less painful nodules appeared on the abdomen and chest. Most of these subsided after several weeks and left brownish spots. Some of them ulcerated and were covered with dark brown crusts. These healed slowly and left deep depressions, which slowly filled in until they were nearly level with the surrounding skin. In May he entered a hospital with jaundice, and pitting edema of the ankles, scrotum and skin up to the xiphoid process developed and lasted five weeks. During the next five weeks more spots developed on his legs, without itching or pain. There was a remittent fever, the highest temperatures reaching 39.5 C (103 F.) on several occasions but usually rising to 38.3 C. (101 F.). The inguinal and the axillary lymph nodes were noted as palpable at this time, but otherwise extensive study failed to reveal the cause or the nature of the patient's illness until an excised lesion was examined histologically by a dermatologist, who suggested a diagnosis of panniculitis or Weber-Christian disease.

Laboratory studies of the blood in June revealed 75 per cent hemoglobin, 4,000,000 erythrocytes and 6,000 leukocytes per cubic millimeter and a sedimentation rate of 10 mm. in one hour. A roentgenogram of the chest made in June showed increased density of the tracheobronchial shadows and broadening of the peripheral bronchi as well, suggestive of an infiltrative process.

As too often happens in diseases of unknown origin, the patient's tonsils were suspected as a cause and excised. Sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was also given, without beneficial effect.

The patient improved for a time at home but was still febrile. The cutaneous lesions subsided. Several weeks later he became worse with high fever and reentered the hospital on September 1. At this time the eruption on the skin reappeared in its most active stage (fig. 1). The spleen was now palpable, and a roentgenogram of the chest showed enlargement and intensification of the hilar shadows and bronchial markings extending to the lower lobe of the right lung resembling the changes seen in pulmonary Hodgkin's disease. The hemoglobin concentration dropped to 65 per cent and the erythrocyte count to 3,000,000. The leukocytes numbered 1,200, of which 69 per cent were polymorphonuclear cells, 20 per cent small lymphocytes and 11 per cent monocytes. The sedimentation rate was 34 mm. in one hour. The patient was then sent to us for further study.

His complaints on entering Jefferson Medical College Hospital in September under our observation were sores on the skin, weakness, intermittent fever, headache and loss of 22.7 Kg. (50 pounds) of weight in seven months.

Physical Examination.—Except for evidence of loss of weight the patient did not seem to be seriously sick. The epitrochlear, the axillary and the inguinal lymph nodes were palpable but not significantly enlarged. The heart and lungs were normal, but the spleen and liver were both enlarged, firm and palpable. There was a faint erythematous eruption about the eyelids and chin, and numerous reddish brown macules of varying shades about 1 to 2 cm. in diameter, mostly about the size of a dime, and some of them depressed occurred on the arms, back, buttocks, abdomen and legs. Several had ulcerated and were covered with

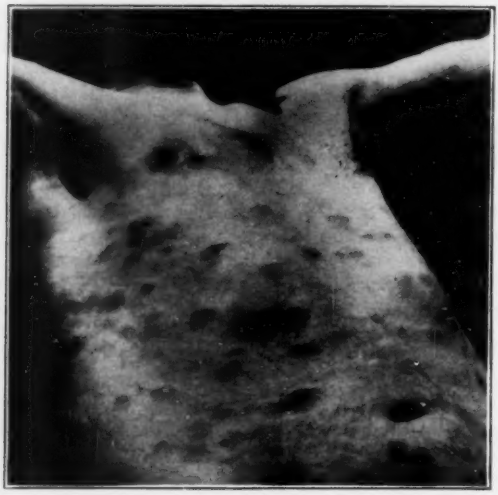

Fig. 1.—Cutaneous lesions at the height of the eruption in the sixth month after onset. Several nodules have ulcerated. Dr. R. P. Batchelor, Palmerton, Pa., permitted us to use this photograph.

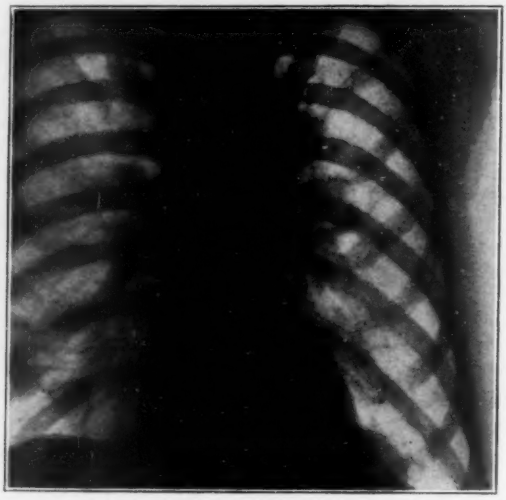

Fig. 2.—Roentgenogram made six months after onset. Note the rounded densities in the lower halves of both pulmonary fields suggestive of metastatic neoplasms. The hilar area is broadened as if by enlarged mediastinal lymph nodes.

black crusts. One deep crust-covered ulcer 5 mm. in diameter was present on the nasal septum. There was an area of brown pigmentation on the left side of the soft palate, but it was impossible to tell whether this was the remains of a lesion. New lesions occasionally appeared as pea-sized, firm, sometimes bright red, tender nodules. A few of the lesions persisted for several months and eventually became necrotic and dry and formed deep ulcers with sharp crater-like edges usually covered with a dark brown or black scab. Healed lesions usually left a yellowish brown discoloration; occasionally, it was permanent and the lesions were slightly depressed or level with the surface of the skin, but usually they left

Fig. 3.—Skin and subcutaneous tissue (× 37.5). Collections of mononuclear cells are present in the derma and in the connective tissue, replacing the fat. The lesions deeper in the panniculus adiposus were much larger. The absence of epidermis in the upper left hand part of the section is an artefact.

no trace at all. It was estimated that more than one half of the total area of skin of the ventral surface of the body and one quarter of that of the dorsal surface had been involved in several relapses since the disease began. The face except for the erythema mentioned, the genitalia, the hands and the feet were free.

There were no physical abnormalities in the chest, but a slight cough which started in July persisted for several weeks. A second roentgenogram made in September (fig. 2), two weeks after the first one, showed round densities in the lower halves of both pulmonary fields, suggestive of metastatic neoplasms, and multiple areas of radiolucency resembling areas of emphysema. The hilar shadows

were broadened, indicating enlargement of the mediastinal lymph nodes. Another roentgenogram of the chest made in October showed general clearing since September, but several new opacities had developed.

Laboratory Data.—Numerous examinations of the blood showed an average of 3,500,000 erythrocytes, 65 per cent hemoglobin and 2,400 to 4,500 leukocytes, of which the granulocytes usually composed about 80 per cent. The platelets

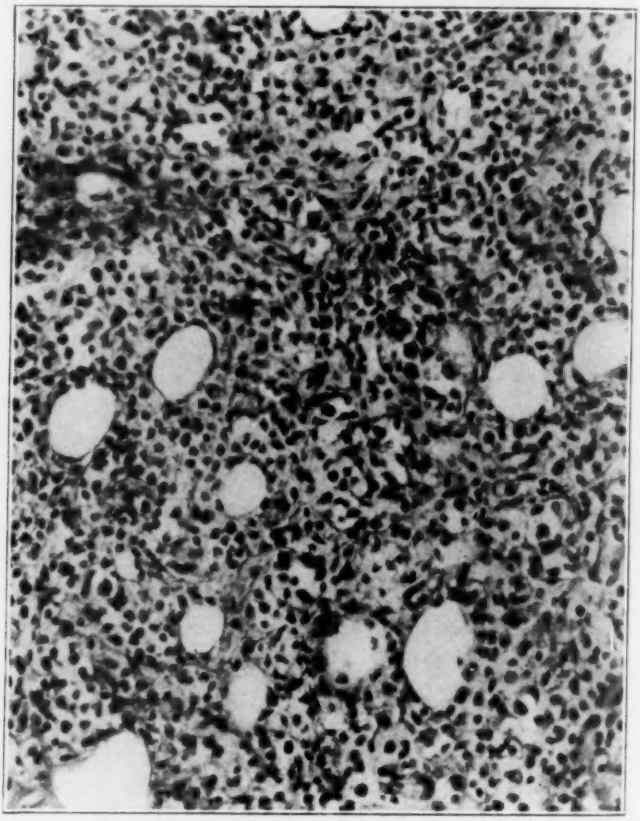

Fig. 4.—Lesions composed chiefly of lymphocytes, plasma cells and mononuclear cells of the Reed-Sternberg type in the panniculus adiposus (× 335).

averaged 190,000 per cubic millimeter. The sedimentation rate was 20 mm. in one hour. The urine was normal; blood cultures, cultures of the tissue removed at biopsy and Wassermann and Kahn reactions gave negative results. The prothrombin was 100 per cent of normal; the result of the direct van den Bergh reaction was positive and that of the quantitative reactions, 1.5 mg.; bromsulphalein injected intravenously was removed from the blood; the urine gave a positive reaction for urobilinogen in a dilution of 1 to 40, and bile pigment was absent

from the urine. The proteins of the blood measured 6.91 mg., of which 3.93 mg. was albumin and 2.98 mg. was globulin. Study of the cells from the bone marrow of the sternum showed hyperplasia of normal leukopoietic tissue.

A new cutaneous lesion and an old one were excised for study. There were no pathologic changes in the epidermis, but in the derma, in the connective tissue and to a greater extent in the subcutaneous fat patchy or nodular, nonspecific inflammatory lesions more or less granulomatous in character replaced the fat (fig. 3). In the derma the lesions collected around small blood vessels sebacious glands and sweat glands. In the subcutaneous tissue (fig. 4) the lesions were composed of fairly extensive, scattered, but not sharply delineated collections of cells, with edema and areas of necrosis. The cells were mostly lymphocytes, with a few plasma cells and rare polynuclear giant cells. The latter were not a conspicuous part of the picture. No lipolytic macrophages were seen, nor were there

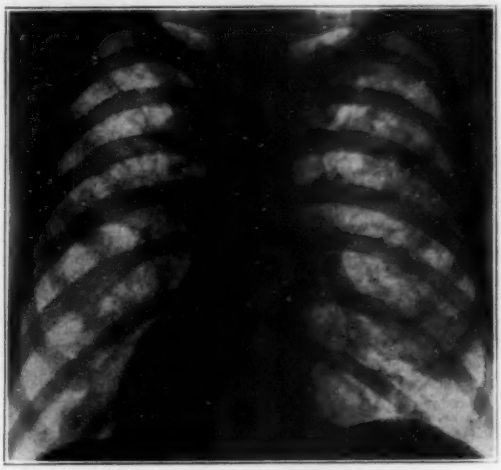

Fig. 5.—Roentgenogram made eight months after onset. As compared with figure 2, it shows a generalized increase in the pulmonary markings, with diffusely scattered flocculent or mottled densities in both pulmonary fields. The nodular densities have faded somewhat.

thrombi or evidence of endarteritis in the small blood vessels in the involved areas. The chief difference between the young and the old lesions was the greater diffusion and the presence of a greater degree of necrosis in the latter. The lesions conformed generally with those described in cases of panniculitis.[1]

The patient was observed at intervals during the next nineteen months. He was weak and failed to regain weight. Isolated nodules appeared in the skin from time to time, coincident with periods of low fever. The spleen and the liver remained palpable and firm. Leukopenia (2,000 to 3,000 cells) and moderate

1. Bailey, R. J.: Relapsing, Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease), J. A. M. A. **109**:1419-1424 (Oct. 30) 1937.

secondary anemia persisted. Tissue taken from the sternal marrow in July 1940 showed hyperplasia and many mononucleated young megakaryocytes. There were occasional slight cough and a surprising absence of abnormal physical signs in spite of the ever changing massive nodular shadows revealed by roentgen examination. These shadows waxed and waned independently of the dermal eruption. Roentgenograms made at intervals are shown in figures 5 and 6.

In January 1941 a pulmonary nodule shown in figure 6 was aspirated. The histologic nature of the tissue was similar to that of the cutaneous lesions (fig. 4) and is shown in figure 7. Heavy exposure of the left lung to roentgen rays failed to cause any change in the size of the nodules.

During the next few months the patient gradually failed; he died at his home in May 1941, about two years after the onset of his illness.

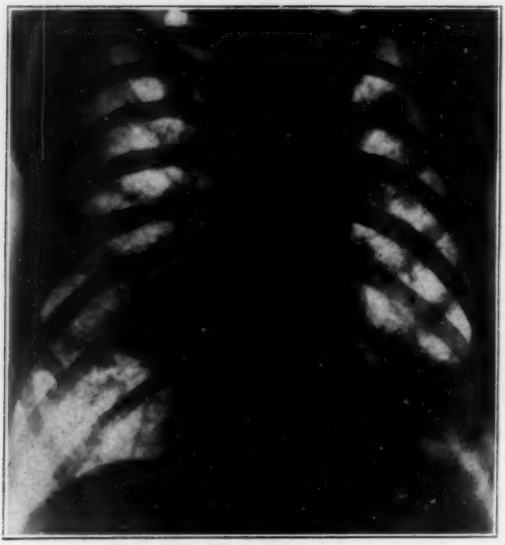

Fig. 6.—Roentgenogram made nineteen months after onset. Large masses are apparent in both lungs. Tissue from the area in the left lung was aspirated for biopsy.

Necropsy.—The lymph nodes of the neck, axillas and groin were not enlarged. There was a superficial cutaneous ulcer 6 by 4 cm. on the abdomen and three cutaneous nodules on the right knee. Both the ulcer and the nodules were similar to the ones already described.

The serous cavities were normal except for a few adhesions in the right pleural cavity. The mediastinal lymph nodes were slightly enlarged, but the cut surfaces showed nothing unusual. The lymph nodes in the mesentery, in the hilus of the liver and along the entire aorta measured up to 2 cm. in diameter. They were firm and matted together, and the cut surfaces were homogeneously pinkish gray except in some nodes where there were necrosis and hemorrhage.

The lungs, kidneys and liver contained scattered tumors. Those in the lungs were situated immediately beneath the pleura and in the outer portions of the parenchyma. They were predominant in the lower lobes. In the kidneys they were situated in the cortices; in the liver they were diffuse. They were firm, gray and sharply circumscribed and measured up to 2 cm. in diameter. Some showed beginning necrosis and hemorrhagic extravasation. In addition, the liver

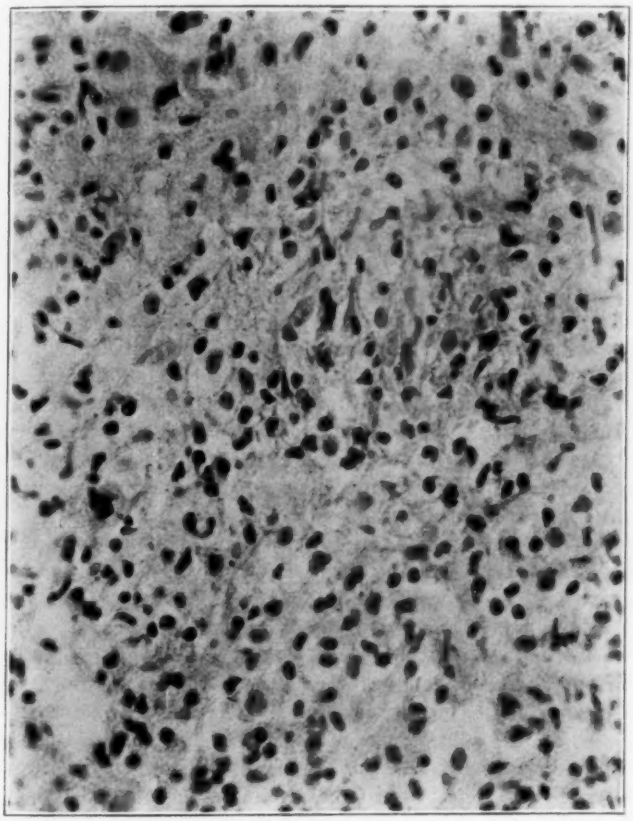

Fig. 7.—Tissue obtained by aspiration of the pulmonary mass shown in fig. 6 (× 500). The lesion is composed mostly of fibrous tissue, with some edema, slight necrosis and inflammatory cells, chiefly lymphocytes, plasma cells and a few monocytes. An occasional eosinophil and rare giant cells are present. Some of the monocytes contain abundant cytoplasm which is lacelike and vacuolated and seems to contain lipid material. The lesion resembles those in the skin (fig. 4).

contained several large masses 4 and 5 cm. in diameter the central portion of which were completely necrotic. The spleen was firm, weighed approximately 700 Gm. and on section was homogeneously dark red.

Histologically, the lymph nodes showed lesions typical of Hodgkin's lymphogranulomatosis. Their normal architecture was completely replaced with pleomorphic cells. These consisted of plasma cells, lymphocytes and other mononuclear cells, a few polymorphonuclear leukocytes and many mononuclear and multinuclear giant cells of the Reed-Sternberg type. There were no eosinophils. There was present, in addition, a varied amount of necrosis and hemorrhage, but fibrosis was not marked.

Necrosis with abscess formation was extensive in the lungs and in the liver and less so in the kidneys. A granulomatous process similar to that seen in the lymph nodes surrounded the necrotic areas. Giant cells, however, were sparse and were chiefly of the mononuclear variety. In the spleen the lymph follicles had almost disappeared. There were some generalized reticular fibrosis and a diffuse infiltration with pleomorphic cells. Reed-Sternberg giant cells, especially the multinucleated type, were numerous. There was no necrosis.

Sections of the cutaneous nodules were essentially the same as those made at biopsy and described previously. Outstanding features were the absence of eosinophils and the paucity of Reed-Sternberg giant cells. The few that were present were almost entirely mononuclear, like those seen in many granulomatous diseases.

COMMENT

As mentioned in the clinical discussion, differential diagnosis was confused. Panniculitis, sarcoid disease, reticuloendothelial cytomycosis (histoplasmosis), toxoplasmosis and mycosis fungoides were considered. Although Hodgkin's disease was early suspected, the histologic changes in the minute portions of tissue from the skin and lungs obtained for biopsy were not in themselves classic or pathognostic enough to confirm the impression. According to Kierland and Montgomery,[2] Reed-Sternberg cells may not be as typical in the skin as they are in the lymph nodes. Therefore, the diagnosis was established only at necropsy when the lesions in the skin and the lungs could be brought into relation with the typical ones in the abdominal lymph nodes.

Furthermore, lesions specific of Hodgkin's disease in the skin are as rare as nonspecific ones are common, and cases in which the first manifestation of the disease appears in the skin are rarer still. The literature on the subject is summarized by Fox,[3] Shelmire,[4] Miller,[5] Senear and Caro,[6] Kierland and Montgomery[2] and others. According to Miller and to Senear and Caro, several examples of "primary" spe-

2. Kierland, R. R., and Montgomery, H.: Cutaneous Ulcerative Hodgkin's Disease, Proc. Staff Meet., Mayo Clin. **16**:124-128 (Feb. 19) 1941.

3. Fox, H.: Lymphogranulomatosis of the Skin in Hodgkin's Disease, Arch. Dermat. & Syph. **2**:578-593 (Oct.) 1920.

4. Shelmire, B.: Hodgkin's Disease of the Skin, South. M. J. **18**:511-518 (July) 1925.

5. Miller, H. E.: Lymphogranulomatosis Cutis: Hodgkin's Disease, Arch. Dermat. & Syph. **17**:156-179 (Feb.) 1928.

6. Senear, F. E., and Caro, M. R.: Ulcerative Hodgkin's Disease of the Skin, Arch. Dermat. & Syph. **35**:114-128 (Jan.) 1937.

cific cutaneous Hodgkin's disease have been reported, but on close scrutiny there is considerable doubt as to diagnosis in some cases and in others the histologic nature of the lesions in the skin was not described. Even in the cases reported by Miller [5] and by Goeckerman and Montgomery [7] there was difficulty in differentiating the condition between mycosis fungoides, lymphosarcoma, leukemia and Hodgkin's disease. The case described here is, therefore, one of the few in which specific lesions in the skin preceded other manifestations of Hodgkin's disease. Two months elapsed before there was clinical evidence of visceral involvement, but whether in our case or in any case the disease can be regarded as strictly primary in skin is, of course, uncertain.

SUMMARY

A case of Hodgkin's disease of two years' duration is reported in which the first evidence of the disease appeared as specific lesions in the skin and fever. Eventually leukopenia, splenomegaly, hepatomegaly and pulmonary infiltration appeared. Abnormal swelling of the lymph nodes was never noted clinically, and at necropsy only the abdominal lymph nodes were involved. Relapsing, febrile, nodular panniculitis was suspected because of the unusual clinical course and dermatologic changes. Diagnosis was established at necropsy when the typical lesions of Hodgkin's disease in the abdominal lymph nodes were associated with the histologic changes in the skin and in the lungs noted at biopsy.

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7. Goeckerman, W. H., and Montgomery, H.: Cutaneous Lymphoblastoma: Report of Two Unusual Cases, Arch. Dermat. & Syph. **24**:383-395 (Sept.) 1931.

Progress in Internal Medicine

VASCULAR DISEASES

EIGHTH ANNUAL REVIEW

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REVIEW OF SOME OF THE RECENT LITERATURE

BY DR. VAN DELLEN AND DR. SCUPHAM

The present review of vascular diseases was compiled from the available literature accumulating between June 1, 1941 and June 1, 1942. A special effort was made to consider those articles which contributed new information, supplemented or confirmed present concepts or offered reasonable explanation of certain phenomena known to exist. This review should not be considered complete, as many deserving articles have undoubtedly been missed. Whenever possible, recognized omissions are usually corrected in a succeeding review. Articles on the dicoumarin 3,3′-methylenebis-4-hydroxycoumarin were not included in this review. They will be considered next year along with many unpublished papers on this drug now known to exist.

The Nomenclature Committee of the Section for the Study of the Peripheral Circulation of the American Heart Association [1] published a list of preferred and universal terms for designating diseases and abnormalities of the blood and lymph vessels of the extremities. Such a standardization of nomenclature is welcome but will undoubtedly be revised from time to time before a final listing will be acceptable to the majority of investigators in this field.

A 461 page monograph was recently published by di Cio,[2] of the University of Buenos Aires. It concerns mainly his experience with

From the Department of Medicine, Northwestern University Medical School; the Department of Surgery, the University of Illinois College of Medicine, and the Circulatory Group, St. Luke's Hospital.

1. Nomenclature: Diseases and Abnormalities of Blood and Lymph Vessels of Extremities, Am. Heart J. **22**:549 (Oct.) 1941.

2. di Cio, A. V.: Enfermedades de las arterias perifericas, Buenos Aires, "El Ateneo," 1941.

400 cases of peripheral vascular disease, including the pathologic aspects, the clinical course and the results of treatment. It also contains a detailed description of the technic used and the results obtained with the author's new procedure for the injection of a carbon dioxide–oxygen mixture. The mixture is used in place of carbonic acid.

PHYSIOLOGY

Reviews.—An excellent review on the physiology of the peripheral circulation is presented by Hertzman.[3] A similar review by Hare and Hinsey[4] on the autonomic nervous system is recommended as being of value to those interested in this aspect of vascular diseases.

Capillaries.—McLennan and his co-workers[5] attempted to devise a new practical method for estimating blood pressure in the minute vessels of human beings during disease. This study was prompted by the many disadvantages of direct measurement of capillary blood pressure by means of a micropipette. A pressure plethysmograph is used, and the effect of graded external pressure on vascular volume is measured. Several pressure volume curves are thus obtained from which is computed not only the volume of blood but the pressure in the minute vessels of the forearm.

Fulton and Lutz,[6] using a microelectrode, stimulated the minute nerves leading to small blood vessels in the retrolingual membrane of the frog. Various united vascular responses were noted, generally dilation followed by constriction. As stimulation of the small nerves in the field of the microscope produced responses which are confined to restricted vascular patterns the authors consider the plexus to be physiologically discontinuous and the concept of smooth muscle motor units in small blood vessels likely.

Di Palma, Reynolds and Foster[7] studied the reactive capability of the smallest blood vessels of the skin by producing local ischemia of sufficient duration to elicit a given degree of reactive hyperemia. For this

3. Hertzman, A. B.: The Peripheral Circulation, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1942, vol. 4, p. 187.

4. Hare, K., and Hinsey, J. C.: The Autonomic Nervous System, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1942, vol. 4, p. 407.

5. McLennan, C. E.; McLennan, M. T., and Landis, E. M.: The Effect of External Pressure on the Vascular Volume of the Forearm, J. Clin. Investigation **21**:319 (May) 1942.

6. Fulton, G. P., and Lutz, B. R.: Smooth Muscle Motor-Units in Small Blood Vessels, Am. J. Physiol. **135**:531 (Feb.) 1942.

7. Di Palma, J. R.; Reynolds, S. R. M., and Foster, F. I.: Quantitative Measurements of Reactive Hyperemia in Human Skin: II. Individual and Seasonal Variations, Am. Heart J. **23**:377 (March) 1942.

study, a series of three weights was applied to an area of skin and observations were made after release. Measurements were accurately calculated in seconds with a stop watch. The authors designated the stimulus time as the minimum period required to produce three areas of ischemia, uniform in color, size and sharpness. The clearing time was considered the time required for the resulting areas of reactive hyperemia to disappear. Average values for normal subjects were obtained.

The authors noted a seasonal variation in the clearing time, which lengthens in the fall, reaching a high level in December. During occlusion of the circulation for five to fifteen minutes with a tourniquet the stimulus time is unaffected, but the areas fail to clear. After release the stimulus time is lengthened. This is explained on the assumption that a dilating substance is released during occlusion but cannot be brought into contact with the blood vessels unless the flow of blood is reestablished. After releasing the tourniquet this substance in the smaller vessels is constantly being washed away, producing a deficit responsible for the local ischemia. Reflex or direct heat shortens the stimulus time, just as warmer weather does.

The capillaries of 8 women suffering from myxedema with typical myxedematous heart disease were studied by Zondek, Michael and Kaatz.[8] In 7 women the capillaries were markedly narrowed and greatly reduced in number, and in some instances only the loops were recognizable. On administration of thyroidin the capillary picture and circulation time gradually returned to normal. The authors are of the opinion that thyroidin is active in opening arteriovenous anastomoses coincidental with increased oxygen requirement.

LeCompte[9] studied the mechanism of the return of vascular tone in denervated ear vessels of rabbits and sympathectomized cats. His results supported the thesis of Grant, who stated the belief that the return of "tone" in sympathectomized blood vessels is due to a return of reactivity or a heightened responsiveness to humoral stimuli. LeCompte failed to find any evidence of a myogenic or intrinsic tone but is of the opinion that the return could best be explained as a response of the sensitized smooth muscle of the vessel wall to circulating vasoconstrictor substances. These substances were most likely epinephrine and sympathin.

In his experiments he utilized as an index of vasoconstriction not only the diameter of the ear vessel but surface temperature. Moderate changes in body temperature had no affect on the denervated vessels, but excitement or struggle produced vasoconstriction. This change

8. Zondek, H.; Michael, M., and Kaatz, A.: The Capillaries in Myxedema, Am. J. M. Sc. **202**:435 (Sept.) 1941.

9. LeCompte, P. M.: Observations on the Return of Vascular Tone After Sympathectomy, Am. J. Physiol. **135**:43 (Dec.) 1941.

was also produced by epinephrine, but acetylcholine and pitressin were not effective. That circulating epinephrine was not entirely responsible was shown by the vasoconstriction produced by struggle in the sympathectomized cats, even though the adrenal glands were removed. In all of the experiments the sympathectomized animals were used promptly to avoid confusing results with those due to regeneration.

Temperature Studies.—Hyndman and Wolkin [10] studied the effects of heat, cold, epinephrine and pilocarpine on the cutaneous reactions of a series of patients who had had various operative procedures performed on the nervous system. Their studies concern three factors in heat regulation by the skin: sudomotor, vasomotor and pilomotor. An attempt was made to ascertain the governing systems, namely, (1) the end organ itself, (2) a reflex through the spinal cord and (3) central (hypothalamic) control. The results were obtained after the patients had been placed in a Burdick fever therapy cabinet, where obvious need for full dissipation of body heat occurred. The authors noted that the fingers and toes exhibit the greatest rise in temperature under these conditions. After unilateral sympathectomy the cutaneous temperatures of the fingers and toes are equal on the two sides after the heat treatment. This occurs regardless of their previous difference, provided these parts are contained in the heating cabinet. From this the authors concluded that the sympathectomized arteriole of the skin is capable of dilating as a result of the effect of heat on the vessel itself. As flushing and sweating occur on the normal side but not on the sympathectomized side, the authors concluded that active dilatation of central origin is the most likely mechanism. These capillary dilator fibers probably course through the anterior roots of the thoracolumbar nerves and thence through the sympathetic ganglions.

Similar studies were performed on these patients after placing them in a refrigerator.[11] The surface temperature was lowered bilaterally, but the sympathectomized side remained a few degrees warmer. That the temperature was lowered bilaterally indicates a local capillary response to cold, but that the normal side was colder indicates a central response. Of interest was the evidence that pain incident to cold is markedly reduced by sympathectomy, which suggested to the authors that the vasodilatation usually incident to sympathectomy does not account for the altered sensation.

10. Hyndman, O. R., and Wolkin, J.: The Autonomic Mechanism of Heat Conservation and Dissipation: I. Effects of Heating the Body; Evidence for the Existence of Capillary Dilator Nerves in Anterior Roots, Am. Heart J. **22**:289 (Sept.) 1941.

11. Hyndman, O. R., and Wolkin, J.: The Autonomic Mechanism of Heat Conservation and Dissipation: II. Effects of Cooling of the Body; a Comparison of Peripheral and Central Vasomotor Responses to Cold, Am. Heart J. **23**:43 (Jan.) 1942.

In both of these reports Hyndman and Wolkin expressed the belief that body temperature under average or ordinary conditions, so far as the skin is concerned, is maintained largely by responses of the vessels themselves to external stimuli. The central mechanism functions (*a*) as a governor over the peripheral mechanism, and hence manifests itself more strongly when the need is extreme, and (*b*) as a device for utilizing or integrating the entire cutaneous surface for conservation or dissipation of heat when only a part is subjected to a changing temperature.

In a third communication Hyndman and Wolkin [12] reported studies on the behavior of the sympathectomized sides of subjects exposed to heat, cold and certain types of pain. They observed a definite alteration of sensation after sympathectomy. When the sympathectomized side was made objectively cold by refrigeration, it was not unusual for a patient to tell the authors that it felt warm. When heat was applied, the side which had been operated on felt slightly cooler than the normal side. The tolerance for cold was greatly enhanced on the sympathectomized side, as the aching and stinging pain normally present on exposure to severe grades of cold was greatly diminished.

Blood Flow.—A critical review of the theory and technic of the plethysmographic method of measuring blood flow was presented by Landowne and Katz.[13] They believe that valuable information can be obtained by this method of study if its limitations are appreciated and the results carefully interpreted. Its many errors are enumerated, but since they cannot be eliminated, certain necessary adjustments are suggested. A workable apparatus is described for studying the volume of blood flow in the human foot and leg, employing the method of Brodie and Russell as used by Hewlett and van Zwaluwenburg. Values for resting and for maximal volume flows in normal subjects are determined. The authors believe that under certain circumstances the caliber of central vessels may be the principal factor which determines the "maximal" volume of blood flow to a region. Their explanation is logical inasmuch as the flow to any region can be no greater than the cross section area of the vessel leading to that part. It can then be assumed that variations in maximal flow under different circumstances may therefore mirror changes in systemic pressure (driving force), express changes in peripheral resistance in the smaller vessels or indicate alterations in central arterial caliber. Under these circumstances patients with hypertension should have a greater flow than normal

12. Hyndman, O. R., and Wolkin, J.: The Sympathetic Nervous System: Influence on Sensibility to Heat and Cold to Certain Types of Pain, Arch. Neurol. & Psychiat. **46**:1006 (Dec.) 1941.

13. Landowne, M., and Katz, L. N.: A Critique of the Plethysmographic Method of Measuring Blood Flow in the Extremities of Man, Am. Heart J. **23**: 644 (May) 1942.

persons, providing the caliber of a vessel remained unchanged and peripheral resistance did not increase. This is precisely what Abramson and Fierst [14] noted. They calculated the rate of resting blood flow in a series of 70 hypertensive and 90 normal subjects. The venous occlusion plethysmograph used was of the same type as that employed in previous studies. In hypertensive patients the flow in the forearm and the leg was greater than that in the control group. Similar responses were not obtained in the hand, as the flow was much less in hypertensive patients. The author concluded that patients with hypertension did not have the generalized and uniformly increased peripheral resistance which was previously thought to exist. They did not take into consideration the "driving force" of an increased blood pressure.

Abramson and Fierst [15] also studied the peripheral vascular responses to ingestion of a predominantly carbohydrate or protein meal. Blood flow was measured with the plethysmograph. The carbohydrate meal elicits no significant changes in the rate of peripheral blood flow in the hand, the forearm or the leg. On the other hand, there is a definite increase in the rate of oxygen consumption, in pulse rate and in pulse pressure. With the protein meal there is initially no change in the peripheral circulation, but later the rate of flow begins to increase, first in the hand and then in the forearm and the leg, usually remaining elevated until the end of the experiment. The changes in oxygen consumption, pulse rate and pulse pressure are similar to those observed with a carbohydrate meal, except that they are of greater magnitude.

Abramson [16] also studied the blood flow to different portions of the extremities following various peripheral vascular responses. The flow to the forearm and the leg is more constant than that to the hand. This is explained by the knowledge that the hand not only contains arteriovenous shunts but is more sensitive to changes in the vasomotor center. This makes the hand less satisfactory than the forearm and the leg for studying the local effect of sudden changes in the systemic circulation.

In association with Katzenstein and Ferris Abramson [17] made certain observations on reactive hyperemia in various portions of the extremities. These authors noted that the estimation of the blood flow repayment after a minute of arterial occlusion is of much greater value than obtain-

14. Abramson, D. I., and Fierst, S. M.: Resting Blood Flow and Peripheral Vascular Responses in Hypertensive Subjects, Am. Heart J. **23**:84 (Jan.) 1942.

15. Abramson, D. I., and Fierst, S. M.: Peripheral Vascular Responses in Man During Digestion, Am. J. Physiol. **133**:686 (July) 1941.

16. Abramson, D. I.: Resting Blood Flow and Peripheral Vascular Responses in Different Portions of the Extremities, J. Mt. Sinai Hosp. **8**:328 (Jan.-Feb.) 1942.

17. Abramson, D. I.; Katzenstein, K. H., and Ferris, E. B., Jr.: Observations on Reactive Hyperemia in Various Portions of the Extremities, Am. Heart J. **22**: 329 (Sept.) 1941.

ing a figure which represents the single maximum response to arterial occlusion (percentage of blood flow debt repaid). In the forearm and the leg, and under certain conditions, in the hand, the magnitude of repayment was found to be directly proportional to the blood flow "debt" which was incurred. In contrast was the effect often noted in the hand, namely, that during the period of reactive hyperemia there was actually a reduction of blood flow to less than the control level. Direct application of heat would often produce a greater increase in blood flow to the hand than could be obtained by a period of arterial occlusion. The authors again considered this lack of uniform response of the forearm, the leg and the hand as indicative of the increased vessel tonus in the hand as compared with that of the forearm and the leg.

Abramson, Schkloven and Katzenstein [18] studied peripheral blood flow in a series of 29 schizophrenic patients, as well as in 23 other subjects with mental disease. In the majority of the psychotic patients the flow was markedly or moderately diminished in the hand but either normal or increased in the forearm and the leg. Exposing an extremity to local heat results in an increased flow in the hand which is equal to that obtained in normal subjects under the same conditions. The authors believe that their studies fail to demonstrate a lesion of the arterial tree at the periphery in the schizophrenic patients or in the other mentally ill patients studied. The reduced blood flow to the hand is again considered to be due to increased vascular tone, which could also explain the conflicting reports obtained in studies on the circulation time.

Stewart and Evans [19] studied peripheral blood flow in 6 patients in a myxedematous state. When the basal metabolic rate was low there was a definite decrease in blood flow, but as thyroid was administered the flow definitely increased. The results of this study are directly opposite to those previously described for hyperthyroidism.

Using the photoelectric plethysmograph, Hertzman [20] was able to demonstrate that the intermediate arteries of the hand, the dorsal metacarpal arteries and the digital arteries, do not participate in the vasoconstrictor reflexes of the hand. The latter reflexes were elicited chiefly by loud noises, immersion of the opposite hand in ice water or the application of cold to the finger studied. Hertzman explained this

18. Abramson, D. I.; Schkloven, N., and Katzenstein, K. H.: Peripheral Blood Flow in Schizophrenia and Other Abnormal Mental States: Plethysmographic Study, Arch. Neurol. & Psychiat. **45**:973 (June) 1941.

19. Stewart, H. J., and Evans, W. F.: The Peripheral Blood Flow in Myxedema as Compared with That in Hyperthyroidism, Am. Heart J. **23**:175 (Feb.) 1942.

20. Hertzman, A. B.: The Relative Responses of the Dorsal Metacarpal, Digital and Terminal Skin Arteries of the Hand in Vasoconstrictor Reflexes, Am. J. Physiol. **134**:59 (Aug.) 1941.

phenomenon by considering the vasomotor reflexes as highly selective with respect to the vascular topography involved in these reactions.

Burch and his associates [21] studied the spontaneous variations in volume of the tip of the right index finger, the tip of the right second toe and the posterosuperior portion of the right pinna on 12 normal white adults. Measurements were made with the plethysmograph, and all changes were considered to arise from intrinsic adjustments rather than as a result of stimuli deliberately applied. All of the parts studied undergo continuous variations in blood volume consisting of at least five separate rhythms. Two of these waves were simultaneous with the heart beat and with respiration, whereas the remaining three were simply designated as alpha, beta and gamma waves.

The mean frequency of the alpha waves is 7.9 per minute in the finger tip, 7.7 in the toe tip and 8.6 in the pinna. The mean volume of the deflections was 14.5 cubic millimeters per 5 cc. of finger, 7.1 cubic millimeters per 5 cc. of toe and 6.6 cubic millimeters per 5 cc. of pinna. The frequency of the beta deflections varied from 1 to 2 per minute and the size from 5 to 60 cubic millimeters per 5 cc. of tissue. The number of gamma deflections varied from 1 to 8 per hour and the volume from 50 to 350 cubic millimeters per 5 cc. of tissue.

The authors were unable to come to any definite conclusions as to the exact significance of these waves. Apparently they are related to functions of the autonomic and the central nervous system and also, probably passively, to the blood pressure. It was noted that in phlegmatic and stable persons the alpha waves were relatively small and varied little in size, whereas in excitable persons they were widespread in size and many were large.

In a second communication [22] a more detailed study of the alpha waves obtained from the records of 5 resting male subjects shows that in a five minute period concordant variations in size of this wave, as well as of the pulse wave, are startlingly low in the finger tips, while the percentage in the toe tips agrees in general with the previous estimates.

In a third article [23] the same authors studied the five types of rhythmic spontaneous variations in senile and in hypertensive patients.

21. Burch, G. E.; Cohn, A. E., and Neumann, C.: A Study by Quantitative Methods of the Spontaneous Variations in Volume of the Finger Tip, Toe Tip, and Postero-Superior Portion of the Pinna of Resting Normal White Adults, Am. J. Physiol. **136**:433 (May) 1942.

22. Neumann, C.; Cohn, A. E., and Burch, G. E.: A Study of the Relationship Between the Pulse and Alpha Waves of the Tips of the Fingers and Toes of Five Adults, Am. J. Physiol. **136**:448 (May) 1942.

23. Neumann, C.; Cohn, A. E., and Burch, G. E.: A Study of Quantitative Methods of the Spontaneous Variations in Volume of the Tips of the Fingers and Toes and Postero-Superior Portion of the Pinna of Hypertensive Patients, Am. J. Physiol. **136**:451 (May) 1942.

The waves were noted to be about the same as in normal subjects with the exception of the volume of the pulse waves to the toes, which was smaller. The latter observation was probably due to arteriosclerotic changes. The alpha waves were of interest. In the hypertensive subjects they resembled the waves observed in emotionally unstable and excitable normal adults, whereas the alpha waves of the senile subjects resembled those of stable subjects. Whether this is due to a sluggish psychosomatic state so well known in senile persons and also whether persons who are emotionally stable and not easily excitable live longer is a problem which was not studied.

Dauber, Weinberg and Landowne [24] studied the effect on pulse rate of applying and releasing occluding cuffs on the lower extremities in 27 normal subjects and 4 patients with thromboangiitis obliterans. Fifty-seven tests, each involving two or more occlusions, were performed with the subject in a horizontal position. Pulse rates were measured from electrocardiographic records. A rapid interruption of the arterial inflow was effected by connecting the wide cuffs, which were placed around the proximal thigh, to a tank of over 200 mm. Hg pressure. The immediate return of flow was assured by disconnecting the pressure tank and opening the cuff tube.

In about one half of the subjects application of the occluding pressure was followed by a slowing in pulse rate of 4 to 20 beats per minute (average 9), developing one to three seconds after occlusion and lasting five to sixteen seconds. During occlusion significant changes in pulse rate did not occur. On release of the occluding pressure a pulse acceleration of 15 to 30 beats per minute was noted in 97 per cent of the subjects, lasting one-sixth to three minutes. This acceleration commenced one to three seconds after release, reaching its maximum in four to five seconds. The extent and the duration of the pulse acceleration varied directly with the length of prior occlusion. No rise in pulse occurred on release of arterial occlusion in the 4 patients with thromboangiitis obliterans.

A fall in arterial blood pressure was observed to follow release of the arterial occlusion, and in 7 subjects studied by direct needle puncture of the brachial artery with a Hamilton manometer, the fall was observed to be instantaneous and the pulse contour changed as expected with a lowering of peripheral resistance. The blood pressure dropped from 12 to 35 mm. systolic and from 14 to 27 mm. diastolic. An instantaneous, transient rise in blood pressure occurred on induction of occlusion in the 5 subjects studied with the same technic.

It is concluded from the time at which the change in blood pressure and in pulse rate occurred that the pulse acceleration on release of

24. Dauber, D. V.; Weinberg, H., and Landowne, M.: Effect on Pulse Rate of Peripheral Arterial Occlusion and Release, Am. J. Physiol. **133**:256 (June) 1941.

peripheral arterial occlusion is a reflex response to the drop in blood pressure and that the latter results from the lowering of the peripheral resistance by reopening the leg vascular channels. The failure of similar pulse acceleration to develop in patients with narrowing of the peripheral vessels would favor this interpretation.

Baldes and his co-workers [25] reported on their ten years' experience with blood flow in trained dogs under various conditions. Some of their work has been published previously but is worthy of repetition. Blood flow was measured with the thermostromuhr method of Rien but with a direct-current heater substituted for the conventional diathermy plates. Technically, they were able to measure blood flow with an error of no more than 10 per cent when the flow was not turbulent. In most of the experiments, the units were applied with the dogs under anesthesia and the studies performed for an indefinite time after recovery from the operation.

In general the flow of blood in a given vessel is directly proportional to the average blood pressure and inversely proportional to peripheral resistance. The velocity of blood flow is difficult to correlate with volume flow unless the size of the cross section of the blood vessel can be ascertained. The authors noted that if the area of cross section is reduced to 11 per cent, the blood flow will still remain more than one half of what it originally was. Rhythmic variations in blood flow were noted in many of the records, and it was concluded that they were due to rhythmic variations in the vascular bed, usually independent of blood pressure and respiration, and aggravated by a sudden noise or an intravenous injection of epinephrine. Exercise or the ingestion of a meal causes a marked increase in peripheral blood flow. Ether anesthesia increases the blood flow, and consequently results of studies made on subjects anesthetized with ether are often misleading. The flow is definitely increased after sympathectomy as well as during experimental thyrotoxicosis. Traumatic shock resulting from the manipulation of the intestines is followed by a definite decrease in flow. Pitressin given intravenously reduces blood flow markedly, but epinephrine produces variable results. It was the hope of the authors that these data will serve to emphasize the fact that blood flow to an extremity is influenced by many factors, any one of which, if altered, may profoundly affect the flow of blood to that region.

The effect of posture on blood flow in the lower extremities has been studied by a number of investigators, with little agreement as to results. Recently, Mayerson [26] reported the results of sixty experiments

25. Baldes, E. J.; Herrick, J. F.; Essex, H. E., and Mann, F. C.: Studies on Peripheral Blood Flow, Am. Heart J. **21**:743 (June) 1941.

26. Mayerson, H. S.: The Influence of Posture on Blood Flow in the Dog, Am. J. Physiol. **136**:381 (May) 1942.

on 20 dogs, using the thermostromuhr to measure blood flow. These animals were anesthetized and tilted to the upright position with feet down. A consistent and marked decrease in the rate of blood flow was noted in the femoral vein and the femoral artery and a less pronounced fall in the carotid artery and the jugular vein. The author believes that the results provided direct evidence that as a result of compensatory orthostatic vasoconstriction there is a slowing of the volume flow to the subcardial regions, with a decrease in renal, gastric and intestinal activity. The decrease in flow on the arterial side is accompanied by a similar decrease in venous return due to pooling and stagnation in the capillaries and veins. The latter decrease is particularly marked if the upright position is maintained for more than relatively short intervals in the absence of adequate vasomotor and muscular tone.

Diagnostic Tests.—An excellent discussion of the value of the various diagnostic tests used in evaluating circulatory disorders was presented by Montgomery, Naide and Freeman.[27] Their study was based on the examination of 1,027 patients, of whom 75 per cent were found to have peripheral vascular disease. The technic and clinical significance of each test are discussed separately. Although history and physical examination are considered most essential, diagnostic tests give information on the degree of obstruction and formation of collateral circulation. In all cases of peripheral vascular disease either damage or repair may become dominant. Collateral circulation means functional repair. Vasodilating tests, the histamine test and reactive hyperemia tests are tests of function, and when past vascular damage is estimated by oscillometry, arteriography or palpation of pulses, these tests help to estimate the extent of collateral circulation. In many cases superimposed abnormal vasoconstriction unfortunately confuses the picture. The authors concluded that only by evaluating the circulation from the standpoint of past damage, its extent and location, repair, functional capacity and superimposed vasomotor tone, can the clinical status of each individual patient be entirely appreciated. Unfortunately, space does not permit a more detailed review of this entire article, but it is recommended to all persons interested in the significance and interpretation of the results obtained from these special tests.

The vasodilating tests for the relief of vessel spasm were also studied by Gootnick, Saland, Klein and Zurrow.[28] They compared the value of (1) the thermal reflex vasodilating test, (2) the sodium nitrite test

27. Montgomery, H.; Naide, M., and Freeman, N. E.: The Significance of Diagnostic Tests in the Study of Peripheral Vascular Disease, Am. Heart J. **21**:780 (June) 1941.

28. Gootnick, A.; Saland, K.; Klein, C., and Zurrow, H.: Studies on Vasodilatation Tests in Peripheral Vascular Disease, J. Lab. & Clin. Med. **27**:878 (April) 1942.

and (3) the peripheral nerve block. Sodium nitrite injected intravenously and the hot water bath were found useful as preliminary tests for vasospasm. The thermal test is better suited for most patients, but the nitrite test is more dependable for patients who give the clinical impression of nonorganic vasospastic involvement. If either of these tests fails to give a normal response, then the nerve block is routinely used. The last-named test usually gives the most reliable information, and in many clinics throughout the country it is frequently used routinely.

Lange and Boyd [29] found fluorescein to be a satisfactory substance for determining circulation time and equally useful in establishing the presence and adequacy of local circulation. When injected intravenously it is nontoxic, and it is devoid of untoward effects when used in large doses. Its presence in the tissues can be easily determined by its fluorescence under ultraviolet light. In occlusive vascular diseases its presence or absence in the tissue is indicative of the blood supply to a given area. This is particularly valuable in ascertaining the level of occlusion. In regard to circulation time its value rests mainly on the fact that its use is an objective test devoid of the defects of other procedures. It is also of value in determining the circulation time in all types of experimental animal.

The authors report on the circulation times obtained on 256 subjects by injecting 2 to 4 cc. of the dye into an antecubital vein and watching for its appearance in the lips, tongue, gums or eyelids. These areas suddenly acquire a greenish yellow appearance under a mercury vapor lamp. The end point is sharply defined. The average circulation time in normal adults is seventeen and one-tenth seconds, in patients with cardiac failure thirty-nine seconds, in patients with hyperthyroidism ten and six-tenths seconds and in patients with hypothyroidism twenty-six seconds. These averages compare favorably with those obtained by established methods. The reviewer has had no experience with this substance, but these results of its use are worthy of consideration.

The application of direct heat to any ischemic limb is not without danger, as it frequently increases pain and accelerates gangrene. De Takáts and Miller [30] recently demonstrated with the plethysmograph that as much increase of blood flow can be obtained by applying indirect heat as by applying a heat cradle directly. This alleviates all of the dangers associated with direct heat and still produces the desired effect. The authors performed all of their studies on patients with different grades of arteriosclerosis, which is wise, inasmuch as this group is most frequently subjected to this form of therapy. A heat cradle of

29. Lange, K., and Boyd, L. J.: The Use of Fluorescein to Determine the Adequacy of the Circulation, M. Clin. North America **26**:943 (May) 1942.

30. de Takáts, G., and Miller, D. S.: Use of Direct Heat and Indirect Heat to Increase Blood Flow to the Extremities, War Med. **2**:429 (May) 1942.

ample size was applied to the root of the affected limb and the abdomen proximal to the level of impaired circulation. Used in this manner it was found to be safe and effective.

Bennett, Hines and Krusen [31] applied short wave diathermy to the trunk of the human body and found it safe and efficient as a means of producing peripheral vasodilatation of the lower extremities. They advocate its use in the management and study of peripheral vascular disease. Although no data were given as to therapeutic results, the authors noted that the increased oral and cutaneous temperatures were not maintained for longer than thirty minutes after the cessation of diathermy. By proper insulation they believed the elevated temperatures could be maintained for several hours or longer. The use of this apparatus to induce reflex vasodilatation was compared with other methods now commonly used. Ten such studies were carried out; in eight of these diathermy succeeded in producing the desired effect, and in two it was obtained more quickly than with other methods of warming.

Various methods of applying diathermy were tried. The authors found the use of an electromagnetic cable in a pancake formation under the lumbosacral region to be the simplest and the most comfortable method of application. It is needless to say that this form of treatment must be given only under careful medical supervision.

Brown and Allen [32] introduced a new heating unit to produce reflex vasodilatation. It is tentatively called a "heating sleeve" or "heating boot" because of its appearance. It consists mainly of fine copper wire woven into a fireproof cloth, which is incorporated into a waterproof and washable cover. A transformer reduces the voltage to 10; a fuse protects against short circuits, and a thermostat included in the unit prevents the temperature from increasing to more than 43 C. The usual methods for testing its value in producing reflex vasodilatation were employed. When applied to one extremity the temperature of the skin of the digits of all the other extremities increases in most instances. The volume flow of blood of the opposite extremities also increases. Clinically, the apparatus is of value whenever controlled heat is indicated.

Effect of Drugs.—Abell and Page [33] used the moat chamber in normal rabbit ears to study the reaction of blood vessels to pressor agents.

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31. Bennett, R. L.; Hines, E. A., and Krusen, F. H.: Effect of Short-Wave Diathermy on the Cutaneous Temperatures of the Feet, Am. Heart J. **21**:490 (April) 1941.

32. Brown, G. E., and Allen, E. V.: Continuous Vasodilatation in the Extremities Produced Reflexly: Physiological Studies on Temperature of Skin and on Volume Flow of Blood, Am. Heart J. **21**:564 (May) 1941.

33. Abell, R. G., and Page, I. H.: The Reaction of Peripheral Blood Vessels to Angiotonin, Renin, and Other Pressor Agents, J. Exper. Med. **75**:305 (March) 1942.

Both renin and angiotonin in small doses cause constriction of the arterioles. Capillaries appear unaffected, while venules exhibit slight constriction or none at all with small doses and moderate constriction with large doses. The flow of blood through the tissues is not reduced except when large doses are administered. Parahydroxyphenylethylamine and methylguanidine sulfate in isopressor amounts act somewhat similarly. Isopressor amounts of epinephrine and pitressin, by contrast, elicit severe vasoconstriction of arterioles lasting longer than that due to angiotonin, but the flow of blood is sharply reduced or abolished altogether. The degree of venular constriction is also greater, while the capillaries remain unaffected. The vasoconstrictor action of angiotonin on the peripheral vessels, studied by this method, is indistinguishable from that of renin, except that it is more rapid. Abell and Page thus concluded that angiotonin is a substance capable of producing hypertension in that it is able to elevate arterial pressure by constricting the arterioles sufficiently to increase peripheral resistance but not sufficiently to reduce blood flow.

Krueger and his associates [34] repeated some of the older experiments on the effect of endocrine substances on gangrene produced by ergotamine tartrate in the tails of adult male and female albino rats. They found that the administration of testosterone propionate or estradiol benzoate does not influence the incidence, extent or rapidity of development of the gangrene in these animals.

According to Schwartz and his co-workers,[35] deproteinated pancreatic extract is relatively nontoxic when injected intravenously into rabbits. In most of the experiments massive doses were employed. The authors believe that the extract could probably be injected safely into human beings but suggest additional experimental work before its use is attempted.

Seldon, Lundy and Essex [36] studied the behavior of the minute blood vessels in the ears of rabbits under the influence of various anesthetic agents. Measurements were made through the Clark window. Simultaneous readings of the systolic blood pressure were also taken. Pentothal sodium lowered the blood pressure and dilated the arterioles and capillaries. Nitrous oxide had just the opposite effect. Cyclopropane

34. Krueger, E.; Ludden, J. B.; Wright, I. S., and Wiland, J.: The Effect of Sex Hormones on the Production of Ergotamine Gangrene in Rats, Am. Heart J. **23**:164 (Feb.) 1942.

35. Schwartz, M. S.; Fisher, M. M.; Wright, I. S., and Duryee, A. W.: Deproteinated Pancreatic Extract (Depropanex): II. Effect of Intravenous Administration in Rabbits, Am. Heart J. **22**:122 (July) 1941.

36. Seldon, T. H.; Lundy, J. S., and Essex, H. E.: Effect of Certain General Anesthetic Agents on Small Blood Vessels in Ear of Rabbit, Anesthesiology **3**:146 (March) 1942.

and oxygen caused an increase in blood pressure and a decrease in the diameter of the arterioles, but the diameter of the capillaries was increased. When a mixture of ethylene and oxygen was used, a slight increase in the systolic blood pressure and a decrease in the diameter both of the arterioles and of the capillaries occurred. Blood circulated through the arterioles with apparently greater velocity during anesthesia with such a mixture than it did during a control period. Ether administered by the drop method increased the blood pressure and decreased the diameter of the arterioles, with an apparent increase in the velocity of the blood stream. The size of the capillaries was also decreased with a decrease in the velocity of the blood stream. The effect of ether is therefore somewhat similar to that of ethylene. The authors believe that the results of these experiments are in keeping with the oozing of blood during anesthesia, with special reference to pentothal sodium anesthesia.

Holman and Hewitt [37] substituted mercuric chloride for uranium nitrate and found that the former substance was also capable of producing necrotizing arterial lesions in dogs. In 1 of the 2 dogs studied an aneurysm developed at the site of one of these lesions.

Hoagland [38] demonstrated with the plethysmograph that the blood vessels of the hindlimb in cats are sensitized to intravenously injected acetylcholine after sympathectomy. After the administration of this drug a marked increase in the blood flow occurred far in excess of the control readings. This was not noted in acute experiments but could be elicited after the fifteenth day following operation. The author emphasizes the necessity of utmost care in doing sympathectomies in cats.

VASOSPASTIC DISORDERS

Leary and Allen [39] reported 4 cases of intermittent claudication apparently resulting from spasm induced by walking. In all of these cases the pulsations in the arteries diminished or disappeared on walking. In 2 cases the patients had aneurysms of the abdominal aorta, whereas in the other 2 the patients had chronic venous insufficiency as a result of previous thrombophlebitis. In no instance could any correlation between the associated pathologic condition and vessel spasm be demonstrated. The authors concluded that spasm must be considered the logical cause of claudication in all patients showing no

37. Holman, R. L., and Hewitt, W. C.: Experimental Necrotizing Arteritis: II. Mercuric Chloride as Effective as Uranium Nitrate in Its Production, Proc. Soc. Exper. Biol. & Med. **49**:58 (Jan.) 1942.

38. Hoagland, H.: Sensitization of Blood Vessels to Acetylcholine by Sympathetic Denervation, Proc. Soc. Exper. Biol. & Med. **48**:326 (Oct.) 1941.

39. Leary, W. V., and Allen, E. V.: Intermittent Claudication as a Result of Arterial Spasm Induced by Walking, Am. Heart J. **22**:719 (Dec.) 1941.

evidence of occlusive vascular disease and having paradoxic reactions in the arteries elicited by exercise. If these conditions are not noted one must consider a localized obliteration of the smaller arteries in the involved musculature as the likely cause.

In keeping with this vein of thought is the work of Freeman and Montgomery [40] on the treatment of intermittent claudication by lumbar sympathectomy. In this study, which is also mentioned in the surgical review, the authors measured the severity of intermittent claudication in 12 patients with obliterative vascular disease of the lower extremities, both before and after blocking the lumbar sympathetic ganglions with procaine hydrochloride. All but 1 of the patients selected for this study presented evidence of abnormal vasoconstriction. The results of this study showed that 7 of the patients demonstrated improvement in their ability to walk, in 3 of them there was subjective improvement and in the remaining 2 no improvement was noted. These results were not adequately explained, and many theories were postulated.

The circulatory status of 8 patients with peripheral neuritis due to dietary deficiency was studied by Wilkins and Kolb.[41] Two additional patients with neuritis due to other causes were also included. Once full reflex vasodilatation was acquired, changes in cutaneous temperatures and blood flow were noted after the application of the various stimuli known to induce vasoconstriction in the digits. The results showed a decrease in the vasomotor tonus of the feet, resembling that occurring after incomplete sympathectomy. A delayed response to vasoconstrictor stimuli was also encountered in the toes of some of the patients. There was no rigid relation between the degree of vasomotor disturbances and the loss of sensation of muscular power. Definite improvement in the vasomotor disturbance usually occurs within two weeks of treatment. A complete return to normal vasomotor function usually requires a longer time.

Mulvey and Riely [42] describe the occurrence in a family group of an interesting syndrome known as status dysraphicus. It is a familial disorder in which the afflicted persons present a variety of degenerative constitutional signs consisting of vasospastic disorders in the extremities, disturbance of sensation in the lower limbs and feet and in a few members similar disturbances in the hands. Anomalies and slow-healing ulcers of the feet were also occasionally noted. It is difficult to distinguish from familial syringomyelia.

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40. Freeman, N. E., and Montgomery, H.: Lumbar Sympathectomy in the Treatment of Intermittent Claudication, Am. Heart J. **23**:224 (Feb.) 1942.

41. Wilkins, R. W., and Kolb, L. C.: Vasomotor Disturbances in Peripheral Neuritis, Am. J. M. Sc. **202**:216 (Aug.) 1941.

42. Mulvey, B. E., and Riely, L. A.: Familial Syringomyelia and Status Dysraphicus, Ann. Int. Med. **16**:966 (May) 1942.

EFFECT OF COLD

In a series of three communications Lewis [43] describes his observations on the effects of cold on the skin and underlying tissues. Cold usually affects normal skin in two distinct ways. It may damage it by direct action, or it may cause it to freeze. The author stresses the distinction between these two effects, as they are commonly described together under the term frostbite. Normal skin can be injured by a reduction of its temperature without the intervention of mechanical injury to the cells. On exposure a local vasodilator substance is released. The resultant reaction is similar to the simplest forms of inflammation, characterized by heat, redness and swelling. The swelling may amount to as much as 15 per cent increase in volume, gradually subsiding in a few hours. Local pain and tenderness are not uncommon. The vasodilating substance is apparently related to the H substance. These are usually acute reactions and relatively transient. Cold allergy is probably related to this group.

The second type of reaction is neither transient nor simple. It includes "chilblains," "erythrocyanosis" (pernio) and "trench foot." All three of these conditions are separately considered but can be regarded as different manifestations of the same process, as all result from the prolonged action of cold. They have a great deal in common. In the early stages there is itching or tenderness, leading to coldness and vascular discoloration and proceeding to swelling, blistering and ulceration. Indolence of the lesions and slowness of healing are common. Their chief distinction lies in their location. Chilblains are found on the hands or other parts undergoing profound exposure. If the legs are involved, the lesions usually appear on the dorsum, especially in women who wear low shoes. Erythrocyanosis (pernio) is common in women and usually develops on the legs; it has been more prevalent since short skirts have been in vogue. In trench foot only the foot is involved after exposure to wet and cold. In the last-named condition freezing weather is not as important an etiologic agent as ordinary coldness with dampness or tight-fitting wearing apparel about the limbs. In all cases multiple exposures are almost as important a causative factor as prolonged exposure. Once any of these conditions has developed, recurrence is usual after exposure to cold of similar or even less severity.

Lewis also discusses the actual freezing of skin under the title of frostbite. This is readily produced by bringing the skin into contact with cold metal or by allowing a jet of cold air to impinge on it. The

43. Lewis, T.: Observations on Some Normal and Injurious Effects of Cold upon the Skin and Underlying Tissues: I. Reactions to Cold and Injury of Normal Skin, Brit. M. J. **2**:795 (Dec. 6) 1941; II. Chilblains and Allied Conditions, ibid. **2**:837 (Dec. 13) 1941; III. Frost-Bite, ibid. **2**:869 (Dec. 20) 1941.

freezing point of skin is determined as being between 0 C. and — 2 C. Since the skin has the property of supercooling, the actual temperature necessary for freezing is much less. Frostbite occurs only when the air is dry and when the ground is snow clad or frozen. Wind favors its occurrence. The nose and ears are usually involved, whereas the feet are relatively free, since they are more commonly protected The longer the exposure the more damage results. The end result of severe freezing, where there is deep penetration of the tissues, is necrosis. In the treatment of frostbite the well known gradual thawing is recommended. The object of this method is to restore the blood flow and warmth gradually and thus avoid vascular and accompanying reactions.

Greene [44] recently noted that the present war has produced two new disorders: immersion foot and shelter foot. The latter was described in last year's review under the term shelter legs. The former is related to frostbite and to trench foot. Its causes are the same, namely, cold, heat after cold, dampness, venous stagnation, wind, anoxia, nutritional deficiency and trauma. As in trench foot, dampness associated with cold and venous stagnation are probably the most important factors in the production of immersion foot. The treatment is similar to that for frostbite and needs no repetition. We find little difference between frostbite, immersion foot and trench foot except in the predisposing causes.

Careful pathologic studies have recently been reported to show that pernio and livedo reticularis are vascular diseases. Although the clinical pictures of these two diseases are different, there is a similarity of the pathologic changes in the arterioles of the skin. Each will be considered separately.

Pernio.—McGovern and Wright [45] describe the clinical picture and results of biopsy in 4 cases of pernio. In all of these cases lowered environmental temperatures resulted in extensive vascular changes in the smaller vessels of the skin, causing anoxemia of the supplied tissue, necrosis and ulceration. In some cases definite scleroderma-like changes ultimately develop. Characteristically, exacerbations of this condition occur in the fall and winter and regression takes place in the summer. In cases of long-standing disease complete recovery may not occur in the summer. Although this condition was considered a tuberculous lesion in the past, no evidence of this disease is found either clinically or roentgenologically. Giant cells were demonstrated in the pathologic sections but were considered to represent a chronic irritative process.

44. Greene, R.: Frost-Bite and Kindred Ills, Lancet **2**:689 (Dec. 6) 1941.

45. McGovern, T., and Wright, I. S.: Pernio: A Vascular Disease, Am. Heart J. **22**:583 (Nov.) 1941.

The authors suggested the following tentative criteria for diagnosis of pernio:

1. It may occur in both sexes, predominantly in females.

2. It usually commences in adolescence or early adulthood.

3. It is associated with cool or cold weather and may show spontaneous recovery in warm weather.

4. The lesions have a predilection for exposed areas, particularly the lower third of the leg, around the internal malleolus and calf. They may extend down to the dorsum of the foot and toes, and up the legs to below the knees.

5. The clinical course of these lesions may be characterized briefly as (a) the formation of a reddened area which later becomes elevated, hard, and very painful; (b) this becomes violaceous and fluctuating; (c) it opens, producing an ulcer; (d) this oozes, drains, and heals, becoming less painful; (e) a violaceous scar remains; and (f) the following winter ulceration tends to recur in the same area.

6. There is a definite pathologic picture. Most characteristic is, first, an angiitis of the smaller vessels; secondly, necrosis of the fat; and, thirdly, the presence of giant cells.

No specific treatment of pernio is known. The authors obtained the best results by triweekly treatments with acetyl-beta-methylcholine chloride by iontophoresis and by protecting the legs from undue exposure with proper clothing. Living in a warm climate should be beneficial.

Barker, Hines and Craig [46] reported on a series of 13 cases of livedo reticularis. This circulatory disorder is characterized by a mottled, blotchy or reticular bluish discoloration of the skin which varies from deep blue when the patient is exposed to a cold environment to red or reddish-purple when he is in a warm environment. There is usually subjective, as well as objective, coldness of the skin. In mild forms the condition is present only during exposure to cold, whereas, in the more severe forms the color persists and is relatively unchanged by environmental temperature. The clinical manifestations differ distinctly from those of Raynaud's disease, acrocyanosis and thromboangiitis obliterans. These patients have no evidence of tuberculosis or syphilis, and the circulatory disturbance develops during adult life. The causation is not known.

Pathologic studies revealed organic changes in the arterioles of the skin, which, with chronic vasospasm, result in regional atony and dilatation of capillaries and slowing of the blood flow. The condition may be complicated by ulceration of the legs and superficial gangrene of the toes. In 2 cases the patients responded well to lumbar sympathetic ganglionectomy.

Raynaud's Disease.—The capillary response in 29 cases of Raynaud's disease was studied by Deutsch,[47] before and after sympath-

46. Barker, N. W.; Hines, E. A., Jr., and Craig, W. M.: Livedo Reticularis: A Peripheral Arteriolar Disease, Am. Heart J. **21**:592 (May) 1941.

47. Deutsch, F.: Capillary Studies in Raynaud's Disease, J. Lab. & Clin. Med. **26**:1729 (Aug.) 1941.

ectomy. All of the measurements were made under a capillaroscope which was equipped for calibration and photography. In addition to the routine observations, the flow in the capillaries was studied after occluding the arterial and the venous flow by the use of a blood pressure cuff quickly pumped up to 30 mm. above systolic blood pressure. The term reflux time was introduced as the time which elapses before capillary flow ceases, whereas the term critical capillary pressure was used to denote that pressure at which the flow once again reappears when the cuff in the foregoing experiment is gradually decompressed at the rate of 10 mm. per two seconds.

On the basis of his studies the author believes that the capillary changes in Raynaud's disease are an earlier manifestation of the disease than the clinical symptoms. He was also able to define the severity of the disease more accurately by this method than by studying the gross clinical findings. In the majority of cases of Raynaud's disease he noted a persistence of the subpapillary plexus and a persistent connection between it and the outgrowing capillaries.

Preganglionic sympathectomy has a distinct influence on the capillary picture of Raynaud's disease. In 12 cases the speed of the blood flow increased. In 10 of 15 cases the width of the capillaries decreased. The author suggests that these changes explain the previously mentioned postoperative pallor and higher temperature of the hand following the surgical procedure. Other changes following operative intervention are as follows: In cases with a slow reflux time, the time increased, and vice versa; the capillary permeability decreased, and the excretory ducts of the sweat glands failed to dilate. As a rule all of these changes became less distinct as time went on. The subjective symptoms of the patient are to some extent independent of this clinical picture, as in some cases the patients were relieved of their complaints but no changes were noted in the capillaries.

Hyndman and Wolkin [48] had the opportunity of studying 3 patients with Raynaud's disease while doing their research on the mechanism of heat conservation and dissipation already reviewed in the section on physiology. Temperature studies were made on these patients after submitting them to the heating and to refrigeration. All had previously had sympathectomies on one side only. The results are not unlike those previously reviewed. The authors are of the opinion that the evidence obtained is greatly in favor of the conclusion that the disease is primarily a vascular and not a sympathetic disorder. Sympathectomy is beneficial objectively because it eliminates the vasomotor influence, which is normal in any given case. It is beneficial subjectively because it abolishes the aching and stinging pain of vasoconstriction. After sympa-

48. Hyndman, O. R., and Wolkin, J.: Raynaud's Disease, Am. Heart J. **23**:535 (April) 1942.

thectomy the hands still retain the local disorder objectively, as cold continues to cause color changes. This was further substantiated by the observation that when a nude subject is placed in a refrigerator and kept long enough to cause a fall in central temperature and at the same time one of his hands is kept at room temperature, the hand does not show evidence of vascular spasm, either subjectively or objectively, even though the exposed hand reacts severely.

Altschule and his associates [49] noted that the lung volume and pulmonary dynamics did not change in 3 patients with Raynaud's disease on exposure to cold. Of the 3 patients studied, 1 had evidence of diffuse pulmonary fibrosis with a striking decrease in pulmonary dynamics under ordinary conditions whereas the other 2 had no evidence of a pathologic condition in the lungs. The authors believe that their findings indicated that the blood vessels of the lungs do not react in a manner similar to those of the hands and feet. These findings were further substantiated by the observation that the circulation time through the lungs did not change on exposure to cold.

ARTERIOSCLEROSIS

An excellent review on the concept of the chemical changes occurring in atheromatosis was recently presented by Page.[50] In this article the author attempts to answer most of the most pertinent questions on the subject. Leary [51] also presented an extensive review on the genesis of atherosclerosis. To review either of these with their many considerations and pathologic studies is not feasible. Leary's summary is worthy of repetition for in it he presents the following evidence:

> That atherosclerosis in man and in the experimental rabbit is due to the presence of excess cholesterol esters within phagocytic cells, which first appear in the intima of the arterial wall.
>
> That cholesterol is esterified in the liver as directly observed in the experimental rabbit.
>
> That cholesterol when fed in excess to rabbits is deposited in the form of esters in the cells of the liver and adrenals.
>
> That the esters as they accumulate in excess become a burden and are removed from these organs by Kupffer cells in the liver and their analogues in the adrenals.
>
> That the cholesterol esters are engulfed as particulate matter by these cells.
>
> That these cells, now lipoid cells, escape from the liver and adrenals through the blood and lymph systems and may produce obstruction in the lymph sinuses.
>
> That lipoid cells, having entered the blood stream, pass through the lung filter and selectively invade the arterial intima. This invasion is favored by stresses but

49. Altschule, M. D.; Linenthal, H., and Zamcheck, N.: Lung Volume and Pulmonary Dynamics in Raynaud's Disease: Effect of Exposure to Cold, Proc. Soc. Exper. Biol. & Med. **48**:503 (Nov.) 1941.

50. Page, I. H.: Some Aspects of the Nature of the Chemical Changes Occurring in Atheromatosis, Ann. Int. Med. **14**:1741 (April) 1941.

51. Leary, T.: The Genesis of Atherosclerosis, Arch. Path. **32**:507 (Oct.) 1941.

is apparently dependent on a positive chemotaxis of the arterial wall for cells carrying cholesterol esters.

That the latent period after the beginning of cholesterol feeding in the rabbit and before aortic lesions appear is dependent on the production of esters in excess and their transport, as indicated in paragraphs 2 to 7 inclusive.

That lipoid cells possess the power to split cholesterol esters and bring the substance into solution in an excess of fatty acids.

That excess cholesterol esters are akin to silica in their irritant character. Both are difficult of metabolism, tend to stay long in tissues and stimulate a growth of connective tissue.

That intravenous silica and cholesterol esters, practically alone among particulate matters, tend to cause in rabbits cirrhosis of the liver, enlargement of the spleen and changes in the kidneys resembling those of chronic "interstitial" nephritis.

That human atherosclerosis is associated with intermittent accretions of excess cholesterol esters in contrast to the continuous accretions in the rabbit fed cholesterol. That the differences in the appearance of atherosclerotic lesions in the two species are due in great part to differences in the manner of feeding. Diffuse lipoidosis is more common in the experimental rabbit, partly for the same reason.

The accepted criteria for the establishment of a causal relation between a given agent and a disease are embodied in Koch's laws. Since animals are not susceptible to all human infections, or because evident parasites cannot be cultivated, or for other reasons, various compromises have been made with these postulates. However, the evidence of a causal relation is most complete when Koch's laws can be satisfied.

In the causation of atherosclerosis the principles of Koch's laws can be fulfilled. Excess cholesterol is always present in the active stages of human atherosclerosis. It can be identified in the lesions as definitely as can the bacterial or other parasitic agents producing infections. It can be extracted from the lesions. Human arterial lesions can be reproduced experimentally by its use with more exactness than the lesions of many human infections can be reproduced by the introduction into susceptible animals of their recognized causal agents. It can be identified in and extracted from the experimental lesions.

Stresses determine the localization of lesions and influence the degree of the sclerotic processes. The efficiency of cholesterol metabolism is modified by sex and thyroid factors. Age (time plus thyroid deterioration) and heredity are also contributing elements.

In another communication Leary [52] suggests that since arteriosclerosis is the "cholesterol disease" of human beings, a diet limited or lacking in cholesterol should prevent arteriosclerosis. Vegetable oils, the sterols which are not absorbed, can be substituted for animal fats.

Wilens [53] has a slightly different idea on the location of atheromatous lesions. He believes that the intimal lipids, whether extracellular or contained within mobile phagocytes, tend as a result of the pulse movements of the vessel to converge or migrate toward points of least mobility, being impeded in their progress at points where firm scars have fused the

52. Leary, T.: Arteriosclerosis, Bull. New York Acad. Med. **17**:887 (Dec.) 1941.

53. Wilens, S. L.: Distribution of Intimal Atheromatous Lesions in Arteries of Rabbits on High Cholesterol Diets, Am. J. Path. **18**:63 (Jan.) 1942.

media to the intima, obliterating potential tissue spaces. Although this idea is not new, it is in opposition to the belief that atheromatous lesions usually develop in places of greater stress and strain. It was Wilens' opinion that since the greatest atheromatous lesions develop in places where the arteries are the least movable, laboratory studies on rabbits could be done to demonstrate this phenomenon. The rabbits were fed cholesterol to stimulate the formation of atheroma, and portions of the femoral and carotid arteries were rendered relatively immobile by being invested in cylindric silver cuffs. The results confirmed his opinion, as the lipids localized in the intima of the arteries in the region of the cuffs in all but 7 of the 36 arteries studied.

Hueper [54] also presented evidence to support the

> . . . thesis that the fundamental and general causal mechanism of degenerative arterial disease is an impaired nutrition and oxygenation of the vascular wall, resulting in endothelial damage, increased intimal permeability, and the infiltration of plasma into the subintimal tissue followed by the proliferation of endothelial cells and the degeneration of the muscular and elastic elements of the media. If the plasma contains persistently or transiently pathologically large amounts of cholesterol or physicochemically related substances forming emulsions with the plasma, there occurs a retention of this material in the proliferating endothelial cells with the ultimate formation of atheromas, representing thus a special morphological variety of arteriosclerosis. The second morphological type of arteriosclerosis, on the other hand, is caused by highly excessive contraction or relaxation of the arterial wall through the action of hypertonic or hypotonic agents, respectively, giving rise to the development of primary medial necroses and calcifications. The secondary calcification of medial necroses is hastened and enhanced, if the primary causal vasculotonic factor (parathyroid hormone, vitamin D) produces at the same time a disturbance in the calcium metabolism or if a high blood calcium level is present normally as in herbivorous animals. Type and dose of the etiologic agents thus influence to a certain extent the morphological type of the resulting arteriosclerotic lesion.

The following etiologic agents are suggested by Hueper: 1. Chemically inert, film-forming and emulsion-forming agents (cholesterol, polyvinyl alcohol, methyl cellulose and, possibly, pathologic, large molecular protein complexes) present in the plasma impair the gaseous and nutritive exchange in the interface of blood and vascular wall. 2. Hypertonic agents cause not only an excessive densification of the vascular tissue with an exaggerated functional and metabolic stimulation of its component elements but a compression of the vasa vasorum resulting in ischemic hypoxemia and aggravating disturbances in the diffusibility of the vascular tissues by nutritive and waste metabolites. These include epinephrine, solution of posterior pituitary, renin, ephedrine, ergot, digitalis and compounds containing lead. 3. By an excessive dilatation of the vascular walls hypotonic agents produce a compression of the

54. Hueper, W. C.: The Etiology and the Causative Mechanism of Arteriosclerosis and Atheromatosis, Medicine **20**:397 (Dec.) 1941.

collapsed vasa vasorum, a slowing of the blood flow and a lowering of the blood pressure, causing thereby stagnant anoxemia in the vascular wall and impaired gaseous exchange between the blood and the surrounding vascular tissues. Histamine, acetylcholine, nitrites, methyl xanthine, caffeine and barbiturates are used. There is also evidence that carbon monoxide and reduced atmospheric pressure may well be included in this group.

Hueper believes that in certain cases a rational therapeutic management of arteriosclerotic patients could be accomplished providing the etiologic agent could be determined. Occupational arteriosclerosis, such as is present in workers employed in tobacco and chemical industries, is amenable to treatment. Iodine preparations and thyroid have proved so far to be the most suitable agents in preventing the development or arresting the progress of arteriosclerosis of various causation. There is, however, no evidence to show that they will cure the disease. The effect of these agents lies purely in the maintenance of an adequate oxygen metabolism, and consequently the best results are obtained when the latter condition is at fault.

Bruger and Rosenkrantz [55] suggest the possible relation of the advent of arteriosclerosis to the decreased activity of the thyroid so commonly associated with advancing age. They reviewed the records of 24,000 determinations of basal metabolic rate and found that 775 were made on patients 55 years or older. Of this group 293 were accepted for analysis. The charts of these patients were studied, and 223 were found to have arteriosclerosis and 70 to be without. A pronounced decrease in the average basal metabolic rate was noted in the former group, especially in patients over 70. Although no definite conclusion is reached, the authors submit many theoretic considerations especially related to the receptibility of the vascular tree to the deposition of lipids the concentration of which depends on thyroid activity.

Masson [56] found that arteriosclerotic vessels have a great affinity for iodine, being somewhat similar in that respect to syphilitic and to tuberculous tissue. All of his experiments were performed on rabbits. Of 6 rabbits who were free from arteriosclerosis 5 were given potassium iodide and 1 was not. In 3 the aorta was free from iodide, and in the other 3 only small quantities could be detected. In another group of rabbits made arteriosclerotic with cholesterol and given iodides, it was always possible to demonstrate a greater iodide content in their aortas than in those of the nonarteriosclerotic group.

55. Bruger, M., and Rosenkrantz, J. A.: Arteriosclerosis and Hypothyroidism: Observation on Their Possible Relationship, J. Clin. Endocrinol. **2**:176 (March) 1942.

56. Masson, P.: Iodine Distribution in Normal and Sclerotic Vascular Walls, Schweiz. med. Wchnschr. **71**:1042 (Sept. 6) 1941.

Ludden, Bruger and Wright [57] continued their studies on experimenal atherosclerosis and found that when female rabbits are fed cholesterol, the development of hypercholesterolemia is inhibited and the deposition of cholesterol in the aorta is prevented by the administration of testosterone propionate or estradiol dipropionate. In male rabbits fed cholesterol these steroids exert little such protective action or none at all.

Daft and his associates [58] give a brief but interesting report on the occurrence of extensive hyaline sclerosis and calcification of blood vessels in 7 young rats observed in the course of some preliminary experiments with purified diets deficient in the vitamin B complex and containing 1 per cent sulfaguanidine (sulfanilylguanidine), supplemented with thiamine, riboflavine, pyridoxine, pantothenic acid, nicotinic acid and choline. This mixture was given continuously for sixty-two to one hundred and ninety-two days prior to autopsy. The sulfaguanidine is considered the etiologic agent.

The incidence and complications of occlusive peripheral arteriosclerosis among diabetic and nondiabetic patients was studied by Dry and Hines.[59] In all cases they assumed arteriosclerosis to be present, as their main concern was to compare the severity or degree of impairment in the two groups. They studied 230 diabetic and 219 nondiabetic patients with conditions given the diagnosis of occlusive peripheral arteriosclerosis. They found that the absolute incidence of arteriosclerosis to a degree of causing arterial insufficiency is significantly higher in the so-called "diabetic group" in every decade when diabetic patients are compared to nondiabetic patients as a group. The ratio for the entire group is approximately 11 : 1. Arteriosclerosis obliterans occurs a decade later among nondiabetic patients as a group than it does among diabetic patients. It occurs two decades later among nondiabetic women than it does among diabetic men, and it occurs one decade later among nondiabetic women than it does among diabetic women. The incidence of arteriosclerosis obliterans among diabetic women is almost eighty times as frequent as it is among nondiabetic women as a group. Even in the age period of as early as 40 to 49 years, arteriosclerosis obliterans is about twelve times as common among diabetic women as it is among nondiabetic men. The ratio of men to women in the nondiabetic group is approximately 7 : 1, whereas the

57. Ludden, J. B.; Bruger, M., and Wright, I. S.: Experimental Arteriosclerosis: IV. Effect of Testosterone Propionate and Estradiol Dipropionate on Experimental Atherosclerosis in Rabbits, Arch. Path. **33**:58 (Jan.) 1942.

58. Daft, F. S.; Ashburn, L. L.; Spicer, S. S., and Sebrell, W. H.: The Occurrence of Hyaline Sclerosis and Calcification of Blood Vessels in Rats on Sulfaguanidine, Pub. Health Rep. **57**:217 (Feb. 13) 1942.

59. Dry, T. J., and Hines, E. A., Jr.: Role of Diabetes in the Development of Degenerative Vascular Disease, Ann. Int. Med. **14**:1893 (April) 1941.

ratio is 2:1 for the diabetic group. The incidence of gangrene or trophic ulcers in the diabetic group is 62.1 per cent and in the non-diabetic group 48.9 per cent. Seventy-nine and four-tenths per cent of the diabetic women have this complication. Diabetic retinitis and diabetic peripheral neuritis also occur with great frequency among diabetic patients afflicted with arteriosclerosis obliterans.

The authors postulate that a biologic background exists for the development of advanced arteriosclerosis in the presence of diabetes mellitus. Apparently, it is an inherent weakness, or an abiotrophy exists which affects both the insulin-producing tissues and the vascular system and which requires in each instance only an additional stimulus to bring about pathologic changes. This stimulus may be obesity, an infectious illness, overfeeding, hypertension or hyperlipemia. Dry and Hines also consider a common mechanism for the production of the frequently associated arteriosclerosis obliterans, retinitis and peripheral neuritis in diabetes. This consists of the involvement of the nutrient vessels, namely, the retinal arterioles in retinitis, the vasa nervorum in neuritis and the vasa vasorum in intimal arteriosclerosis.

Kauvar [60] also believes that arteriosclerosis and the resultant ischemia represent a major cause in the production of diabetic neuritis. His data were obtained from a study of 150 patients, of whom 65 had diabetes, 80 had generalized arteriosclerosis and 5 had a deficient blood supply to the extremities not due to arteriosclerosis or diabetes. In this study evidence of peripheral neuritis was found in 18 per cent of the patients with diabetes, in 8 per cent of the patients with generalized arteriosclerosis without diabetes and in all the patients with grossly deficient blood supply to the extremities.

Meyers and Altshuler [61] tabulated the incidence of peripheral vascular disease in 74 diabetic patients. Thirty-two (43 per cent) were found to have varying degrees of vascular insufficiency. Of this group, 13 (41 per cent) had no symptoms but showed evidence by careful study. The incidence of this complication increased with the age of the patient, but no correlation was observed between the severity of the diabetes and the presence of peripheral vascular disease.

That serum potassium is the substance responsible for pain in ischemic tissue was considered likely by Harpuder and Stein.[62] They arrived at this conclusion by studying a sample of blood drawn from an antecubital vein after ischemic exercise of the arm. Samples were

60. Kauvar, A. J.: The Relation of Arteriosclerosis to Diabetic Neuritis of the Lower Extremities, J. Clin. Endocrinol. **1**:955 (Dec.) 1941.

61. Meyers, M. P., and Altshuler, S. S.: Peripheral Vascular Studies of the Lower Extremities in Diabetic Patients, Harper Hosp. Bull. **1**:40 (Dec.) 1941.

62. Harpuder, K., and Stein, I. D.: Studies on the Cause of Pain in Ischemia, Arch. Phys. Therapy **23**:218 (April) 1942.

taken (1) during rest, (2) ten seconds after ischemic exercise and release of circulation and (3) three minutes later. Of many substances investigated, potassium was the only chemical to increase during exercise, being 20 to 25 per cent higher during this period. As details concerning the number of cases investigated and the exact chemical figures are not included, little can be said concerning the authenticity of this hypothesis.

EMBOLISM AND THROMBOSIS

Garvin [63] investigated the relative importance of mural thrombi as a source of emboli. He studied the problem indirectly on the assumption that if mural thrombi are an important source of emboli, then patients having mural thrombi should have a significantly higher incidence of infarction of the various viscera than a control group would have.

He then examined the clinical and pathologic records of 771 consecutive adult patients who died of heart disease and were examined post mortem. The incidence of pulmonary infarction was found to be three times as frequent in those patients with mural thrombi in the right side of the heart as in those patients without. Infarcts of the brain, kidneys, spleen, intestines and extremities were more than twice as common in patients with mural thrombi in the left side of the heart as in patients without such thrombi in this location. These observations were indicative to the author that mural thrombi in the heart are a significant cause of embolic occlusion of arteries both in the lesser and in the greater circulation.

There is increasing evidence that arterial obstruction rather than venous obstruction plays a significant role in the causation of Volkmann's contracture. Horwitz' [64] recent studies lend support to this concept in that he was able to demonstrate a widespread venous anastomosis in the elbow region in normal persons which was not only well protected between the muscle planes but external to the confines of the antecubital space.

In the present review we have not attempted to cover the literature on cervical ribs and thrombosis of subclavian vessels. A case reported by Hoobler [65] was of interest. A patient had cervical ribs and throm-

63. Garvin, C. F.: Mural Thrombi in the Heart as a Source of Emboli, Am. J. M. Sc. **201**:412 (March) 1941.

64. Horwitz, T.: The Significance of the Venous Circulation About the Elbow in the Pathomechanics of Volkmann's Contracture, Surg., Gynec. & Obst. **74**:871 (April) 1942.

65. Hoobler, S. W.: The Syndrome of Cervical Rib with Subclavian Arterial Thrombosis and Hemiplegia Due to Cerebral Embolism, New England J. Med. **226**:942 (June 11) 1942.

bosis of the right subclavian artery which was complicated two years later by hemiplegia due to a cerebral embolism.

Aggeler, Lucia and Thompson [66] described a syndrome resulting from the occlusion of all of the vessels arising from the arch of the aorta. The condition was characterized by complete absence of pulsations in carotid arteries and in the arteries of both upper extremities. Symptoms referable to the central nervous system, ocular manifestations, atrophic rhinitis and atrophy of the arms and legs are usually present. In the case described by these authors the exact causation was not known, but the condition was thought to result from thrombocytosis and autohemagglutination.

Cases of gangrene of a digit secondary to local anesthesia were reported by McLaughlin [67] and Pelner.[68] This unfortunate complication prompted the latter author to investigate the effect of injection of various anesthetic agents into the base of a rat's tail. Thirty male rats were given injections of 1 and 2 per cent procaine hydrochloride with epinephrine in the concentrations usually marketed or without epinephrine at all, as well as with physiologic solution of sodium chloride and with epinephrine in a concentration of 1 : 10,000. No cases of gangrene of the tail were encountered in the rats given injections either of 1 or of 2 per cent procaine hydrochloride or of saline solution. Of the remaining 21 rats, gangrene of the tip of the tail developed in 10 within thirty-six hours after receiving procaine hydrochloride with epinephrine. The author concluded that epinephrine should not be used in anesthetic mixtures in any concentration for operations on the fingers or toes.

Gangrene of the extremities in the newborn has been occasionally encountered. Recently Heller and Alvari [69] reported a case of such a condition in which the causation remained obscure. They believe that it was either due to pressure on the limbs from a long and difficult labor or secondary to infection.

AINHUM

A case of ainhum is reported by Davies and Hewer.[70] In this case the patient was a 55 year old Negro with evidence of generalized

66. Aggeler, P. M.; Lucia, S. P., and Thompson, J. H.: A Syndrome Due to Occlusion of All Arteries Arising from the Aortic Arch, Am. Heart J. **22**:825 (Dec.) 1941.

67. McLaughlin, C. W.: Postoperative Gangrene of the Finger Following Digital Nerve Block Anesthesia, Am. J. Surg. **55**:588 (March) 1942.

68. Pelner, L.: Gangrene of the Toe, Following Local Anesthesia with Procaine-Epinephrine Solution, New York State J. Med. **42**:544 (March 15) 1942.

69. Heller, G., and Alvari, G.: Gangrene of the Extremities in the Newborn, Am. J. Dis. Child. **62**:133 (July) 1941.

70. Davies, J. N. P., and Hewer, T. F.: Ainhum: Report of a Case in England with Histological Study, Tr. Roy. Soc. Trop. Med. & Hyg. **35**:125 (Sept.) 1941.

vascular disease and intermittent claudication, but histologic study demonstrated that the changes in the little toes were of local origin and in no way suggestive of arteriosclerotic gangrene. The authors suggest that epidermophytosis might lead to such lesions, even though no fungus could be demonstrated in this case.

THROMBOANGIITIS OBLITERANS

Thompson [71] stresses the relation of dermatomycosis not only to thromboangiitis obliterans but to thrombophlebitis, phlegmasia alba dolens, migratory phlebitis and postphlebitic ulcer. Rather than consider a superficial mycosis as being merely incidental, the author has reason to believe that this infection may play a more vital role, possibly providing the etiologic agent for the vascular disorder itself. Even though there is no evidence to incriminate fungi directly, the vessels and deeper tissues may react in a manner similar to the well recognized allergic reaction of tissue elsewhere to the products of these organisms. As examples, reference is made to the dermatophytid and the characteristic "tuberculin type of reaction."

Naide [72] also shares this opinion with Thompson. Of his series of 30 patients with thromboangiitis obliterans, 28 (93 per cent) had dermatophytosis clinically, severe in 20. Of 30 controls, men between the ages of 20 and 50 without thromboangiitis obliterans, 22 (73 per cent) had dermatophytosis clinically, severe in 9. Vesicles, extensive scaling, fissures and involvement of nails were definitely more common among patients with thromboangiitis obliterans than among the controls. On microscopic examination fungi were found in 5 to 12 patients with Buerger's disease, a proportion usually obtained in all patients with dermatophytosis. The trichophytin test was also revealing. Cutaneous tests were made with trichophytin (1:30) on 30 patients with thromboangiitis obliterans. After forty-eight hours 24 patients (80 per cent) gave positive reactions to trichophytin. Of the 30 controls, 6 (20 per cent) gave positive reactions. Of the 8 controls without clinical evidence of dermatophytosis, none gave a positive reaction.

Ten of the patients were observed during attacks of migratory phlebitis. Seven of these had an exacerbation of dermatophytosis preceding the attack of phlebitis. The author is in agreement with Thompson that the evidence to date is insufficient to suggest an etiologic relation between the two diseases, but he believes that certain clinical features of thromboangiitis obliterans are more readily accounted for

71. Thompson, K. W.: The Relationship of the Dermatomycoses to Certain Peripheral Vascular Infections, Internat. Clin. **2**:156 (June) 1941.

72. Naide, M.: The Causative Relationship of Dermatophytosis to Thromboangiitis Obliterans, Am. J. M. Sc. **202**:822 (Dec.) 1941.

on the basis of fungous infection than by other etiologic mechanisms thus far proposed. This theory should not be disregarded, but additional study is necessary before acceptance.

That cardiac disease is not uncommon in patients with thromboangiitis obliterans has apparently been well established. On the other hand, surprisingly few cases of coronary thrombosis secondary to this disease have been reported. A case of such an occurrence was recently submitted by Greenfield,[73] but since the patient in this case survived, definite pathologic proof is lacking. From the literature cited by Greenfield one wonders if the incidence of involvement of the coronary arteries is as great as previously considered.

No mention is made of the possibility of coexisting arteriosclerosis, as many patients with Buerger's disease live sufficiently long for degenerative changes to develop. It is our opinion that changes in the electrocardiograms of patients with long-standing thromboangiitis obliterans are, in many instances, secondary to coronary sclerosis. The possibility of arterial disease predisposing one to arteriosclerosis must also be considered.

On reporting 4 cases of thromboangiitis obliterans involving the arteries of the brain, Antoni[74] suggested that this condition might be more common than previously considered, as in many cases the condition has undoubtedly been given the incorrect diagnosis of juvenile arteriosclerosis.

Three cases were presented by Silbert[75] in which thromboangiitis obliterans and polycythemia occurred in association in the same patient. This combination is so rare that Silbert considered it coincidental. Fatherree and Hurst[76] report the association of thromboangiitis with scleroderma. This combination was not only unusual in itself but of interest in that the scleroderma developed after cervicothoracic sympathectomy.

Thromboangiitis in Negroes is probably more common than the literature leads one to believe. A case was recently reported by Warshawsky.[77]

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73. Greenfield, I.: Coronary Artery Thrombosis, with Recovery, in a Case of Thromboangiitis Obliterans, Am. Heart J. **22**:707 (Nov.) 1941.

74. Antoni, N.: Buerger's Disease, Thrombo-Angiitis Obliterans, in the Brain: Report of Four Cases, Acta med. Scandinav. **108**:502 (Oct.) 1941.

75. Silbert, S.: Thrombo-Angiitis Obliterans and Polycythemia Vera, J. Mt. Sinai Hosp. **8**:1021 (Jan.-Feb.) 1942.

76. Fatherree, T. J., and Hurst, C.: Thromboangiitis Obliterans and Acrosclerosis, Northwest Med. **40**:200 (June) 1941.

77. Warshawsky, H.: Thromboangiitis Obliterans in the Negro: Report of a Case, M. Bull. Vet. Admin. **18**:83 (July) 1941.

PERIARTERITIS NODOSA

Twenty additional cases of periarteritis nodosa were reported during the past year.[78] The numerous articles on this disease have undoubtedly made clinicians more conscious of its occurrence, resulting in more frequent diagnosis. Felsen made the diagnosis in 1 case prior to death by a sigmoidoscopic study. He noted peculiar horizontal linear dark red streaks running in parallel lines in the rectosigmoid area. Careful study with a telescopic device revealed that these lesions were within the vessels and that the widened areas within the vessels were thrombotic. Subsequent study at autopsy confirmed his observations.

TEMPORAL ARTERITIS

Four cases of temporal arteritis were reported this year.[79] No new comment was made on the causation or on the characteristics of the pathologic picture.

Gilmour [80] cites 4 cases of a rare and little known form of arteritis. Syphilis was excluded in 3 of his cases, and in most of those reported in the literature. Tuberculosis is also excluded. The essential microscopic change is inflammation, and the prodromal symptoms are strongly suggestive of infection. The microscopic and the clinical features do not resemble those encountered in other types of arteritis. The author believes that the disease is probably a separate entity. In the branches of the arch of the aorta and in the internal and the external carotid

78. Keith, H. M., and Baggenstoss, A. H.: Primary Arteritis (Periarteritis Nodosa) Among Children, Proc. Staff Meet., Mayo Clin. **16**:568 (Sept. 3) 1941. Blaisdell, E. R., and Porter, J. E.: Healed Stage of Periarteritis Nodosa: Report of Case, New England J. Med. **224**:1087 (June 26) 1941. Foster, D. B., and Malamud, N.: Periarteritis Nodosa, Univ. Hosp. Bull., Ann Arbor **7**:102 (Dec.) 1941. Jones, G. M.: Periarteritis Nodosa, with Case Reports, Ann. Int. Med. **16**:920 (May) 1942. Stewart, A. M.: Periarteritis Nodosa, Proc. Roy. Soc. Med. **35**:18 (Nov.) 1941. Malamud, N., and Foster, D. B.: Periarteritis Nodosa, Arch. Neurol. & Psychiat. **47**:828 (May) 1942. Spalding, J. E.: Periarteritis Nodosa and Its Surgical Significance: Report of a Case, Guy's Hosp. Rep. **90**:234, 1940-1941. Maxwell, E. S., and Maxson, W. T.: Cerebral Type of Periarteritis Nodosa: Case Report, Internat. Clin. **2**:217 (June) 1941. Williams, R. R., and Zeek, P.: Periarteritis Nodosa with Peripheral Polyneuritis and Hyperglycemia, Ohio State M. J. **38**:148 (Feb.) 1942. Lund, H. Z.: Periarteritis Nodosa, ibid. **38**:244 (March) 1942. Coe, M.; Reisman, H. A., and DeHoff, J.: Periarteritis Nodosa in a Nine-Year-Old Child, J. Pediat. **18**:793 (June) 1941. Felsen, J.: The Sigmoidoscopic Diagnosis of Periarteritis Nodosa, Ann. Int. Med. **15**:251 (Aug.) 1941.

79. Hoyt, L. H.; Perera, G. A., and Kauvar, A. J.: Temporal Arteritis, New England J. Med. **225**:283 (Aug. 21) 1941. Scott, T., and Maxwell, E. S.: Temporal Arteritis: A Case Report, Internat. Clin. **2**:220 (June) 1941.

80. Gilmour, J. R.: Giant-Cell Chronic Arteritis, J. Path. & Bact. **53**:263 (Sept.) 1941.

artery the disease is focal, bilateral and symmetric, while in the aorta it is usually widespread. The inflammation apparently heals in time, but death has occurred from rupture of an aneurysm or from thrombosis during active inflammation. Multinuclear giant cells are present in most of the affected vessels, and consequently the author gives this disease the name of giant cell chronic arteritis.

Neel and Herrmann [81] report a case of sudden occlusion of the major vessels to the left leg by a large embolus originating in an area of tuberculous thrombophlebitis of the pulmonary vessels. This was confirmed at autopsy, but of interest were the associated metastatic foci of tuberculous arteritis.

Fite [82] noted that in the cutaneous lesions in 32 of 77 cases of leprosy, some involvement of the blood vessels was present, usually with bacilli in the lining of endothelial cells. Infection of the terminal vascular loop was the most common occurrence, whereas the larger vessels were involved in a variety of ways. Arteries and veins were involved with equal frequency.

VASCULAR TUMORS

Thirteen cases of glomus tumors were reported during the last year.[83] Of interest were the 4 cases collected by Kaufman and Clark from the same family.

Thomas [84] reports on the pathologic and clinical analysis of 27 cases of benign and of malignant vascular tumors involving bone. This study was made possible through the cooperation of the Bone Sarcoma Registry of the American College of Surgeons, proving the value of

81. Neel, W., and Herrmann, L. G.: Tuberculous Peripheral Arteritis Associated with Tuberculous Thrombophlebitis in the Lungs, Am. Heart J. **22**:702 (Nov.) 1941.

82. Fite, G. L.: The Vascular Lesions of Leprosy, Internat. J. Leprosy **9**:193 (April-June) 1941.

83. Kaufman, L. R., and Clark, W. T.: Glomus Tumors, Ann. Surg. **114**: 1102 (Dec.) 1941. Jaeger, J. R., and Kingry, C. B.: Glomus Tumor, Rocky Mountain M. J. **38**:717 (Sept.) 1941. Monserrat, J. L.: Tumor glomico de la concha del pabellion auricular, Rev. argent. de oto-rino-laring. **9**:173 (May-June) 1940. Milch, H.: Pressure Atrophy of Terminal Phalanx Due to Subungual Glomus, Bull. Hosp. Joint Dis. **2**:128 (July) 1941. Beaton, L. E., and Davis, L.: Glomus Tumor: Report of Three Cases; Analysis of Two Hundred and Seventy-Four Reported Cases, Quart. Bull. Northwestern Univ. M. School **15**:245, 1941. Murray, M. R., and Stout, A. P.: The Glomus Tumor, Am. J. Path. **18**:183 (March) 1942. Loeb, M. J.: Trauma and Glomus Tumors, Indust. Med. **10**: 208 (May) 1941. Rypins, E. L.: The Roentgenologic Aspects of Subungual Glomus Tumor, Am. J. Roentgenol. **46**:667 (Nov.) 1941.

84. Thomas, A.: Vascular Tumors of Bone: A Pathological and Clinical Study of Twenty-Seven Cases, Surg., Gynec. & Obst. **74**:777 (April) 1942.

such a registry for studying rare conditions. All of the tumors were true endotheliomas, mesenchymal in type, arising from congenital rests by a process of endothelial proliferation and differentiation into new blood vessels. The typical benign angioma is a highly differential structure composed of fully developed blood vessels which grows slowly and with little evidence of cellular activity. As the symptoms are not pathognomonic the diagnosis is usually established by roentgen examination. The characteristic roentgenograms vary depending on whether vertebrae or flat or long bones are involved. Treatment is quite successful by irradiation or operation or both.

The malignant angiomas are characterized by rapid growth, invasion of surrounding tissue and sometimes metastasis. They consist of highly cellular angioblastic tissue, which in its histogenesis tends to revert to the original primitive mesenchymal structure, producing a varied histologic picture differing greatly from the well differentiated benign forms. There is always present an angioblastic tendency evidenced by endothelial proliferation and the formation of new blood vessels. Diagnosis is difficult, as malignant angiomas possess few characteristic roentgenographic or clinical features. Diagnosis is based largely on their histologic appearance. They are only moderately radiosensitive, and early diagnosis and radical surgical treatment are essential for cure.

Four cases of venous angioma of skeletal muscle were reported by Fulton and Sosman.[85] In these cases the diagnosis was made by the roentgen demonstration of phleboliths in the tumor. The authors believe that the finding of multiple phleboliths in areas of the body where normally no plexus of veins exists is practically pathognomonic of a venous angioma. This is particularly true in the extremities.

EDEMA

The mechanism of edema formation in failure of the right side of the heart was studied by Fahr and Ershler.[86] It was found to be due to the rise in capillary hydrostatic pressure rather than to anoxemia. Edema develops when the hydrostatic pressure in the venous end of the capillaries rises to within 2 mm. or less of the colloid osmotic pressure. This is particularly true if a patient is up and about, if no precautions are taken as to salt and water restriction and if no diuretics are given. When the colloid osmotic pressure is normal, 22 mm. of mercury, a tendency toward edema is present when the hydrostatic pressure in the venous end of the capillaries is 20 mm. of mercury or

85. Fulton, M. N., and Sosman, M. C.: Venous Angiomas of Skeletal Muscle, J. A. M. A. **119**:319 (May 23) 1942.

86. Fahr, G., and Ershler, I.: Studies of the Factors Concerned in Edema Formation: II. The Hydrostatic Pressure in the Capillaries During Edema Formation in Right Heart Failure, Ann. Int. Med. **15**:798 (Nov.) 1941.

the venous pressure in the arm veins is 13 mm. of mercury. A drop in colloid osmotic pressure of 7 mm. of mercury or a rise in capillary pressure of 8 mm. of mercury produces approximately the same tendency toward edema. A tendency toward edema is also present when the colloid osmotic pressure is not more than 9 mm. higher than the venous pressure in the arm.

A case of unilateral hypertrophy of the leg due to venous retardation was described by Luke.[87] A thorough study was made as to the cause of this enlargement, as it resembled clinically an instance of venous congestion. In this case the patient had been previously healthy and gave no history of phlebitis. There was no evidence of lymphatic blockage. The diagnosis was finally established by roentgenograms made after the injection of diodrast. This study revealed the absence of, or defective valves in, the deep venous system of the involved leg. The author considered that venous pressure caused the hypertrophy of the leg. Apparently this extremity was endowed with a set of valves congenitally weaker or numerically fewer than normal.

TREATMENT

Assuming that an increase in blood volume should benefit patients with deficient circulation led Hayward[88] to investigate the possibility of intravenous administration of serum in the treatment of peripheral vascular disease. Fifty transfusions were given to 16 patients suffering from a variety of peripheral vascular disorders, mainly of the occlusive type. Each transfusion consisted of 800 cc. of pooled liquid serum having a protein content of 7 per cent. Reactions were few, although chills and fever occurred on fifteen occasions. After transfusion the blood volume increased markedly, gradually returning to normal after two to three days. The oscillometric readings and cutaneous temperatures apparently increased. The response to reflex vasodilatation was greater after transfusion than before. The results of these special studies are not clear. As an example, the serum did not increase the surface temperature if the skin was cold but did so if the skin was warm. In 3 patients the reflex method of producing vasodilation failed to produce a response prior to the administration of serum, whereas after serum was given a normal response was elicited. One questions the technic,

The clinical results were good. In all, 7 of 10 patients with cold limbs had improvement in the warmth of the limb; in the remaining 3 there was little increase in warmth. Of the 8 patients with pain at

87. Luke, J. C.: The Diagnosis of Chronic Enlargement of the Leg, with the Description of a New Syndrome, Surg., Gynec. & Obst. **73**:472 (Oct.) 1941.

88. Hayward, G. W.: Intravenous Serum in the Treatment of Peripheral Vascular Disease, Brit. M. J. **1**:285 (Feb. 28) 1942.

rest, all were relieved; in 6 it was complete after the first transfusion and in 2 only after three transfusions. The walking distance of 4 of 6 patients with intermittent claudication was improved. One of the 3 patients with Raynaud's disease improved. Pregangrenous color changes improved in 4 patients. All of the 6 patients with ulcers of limbs associated with chronic arterial disease recovered after one to three transfusions.

The author was of the opinion that the action of intravenously administered serum was purely mechanical, produced by the increase in blood volume which follows the transfusion.

Linton and his associates,[89] using a perfected thermostromuhr, presented laboratory evidence that therapeutic venous occlusion increased the arterial blood flow to the hind extremity of dogs. The increased flow occurs during the time of occlusion but returns to normal when the pressure is released. A pneumatic tourniquet produces a greater inflow of blood than ligation of the main vein from the leg. The increase in blood flow appears to be directly related to the height of the venous pressure up to a certain level, above which the arterial inflow begins to decrease. These results were obtained with patent, as well as occluded, arteries, although in the latter the maximum flow occurred much less rapidly. As the flow increased only during the period of venous occlusion, the authors are of the opinion that in the treatment of arterial occlusion by intermittent venous congestion the period of venous obstruction should be longer than the period of release. By studying the blood flow in one extremity while venous occlusion was produced in the contralateral one, it was shown that the increase in the arterial blood flow is probably not caused by a humoral or a nervous mechanism. The authors expressed the opinion that a mechanical dilatation was the most likely explanation for this phenomenon.

Horton, Krusen and Sheard [90] studied the effect of various mechanical devices currently used in the treatment of peripheral vascular diseases on the surface temperatures of the toes. Normal subjects, as well as patients with peripheral vascular diseases, were used in their experiments. From their results they concluded that neither the pavaex machine nor apparatus for intermittent venous occlusion is capable of promoting increased blood flow in normal extremities or of value in treating persons with peripheral vascular disease. The best results were obtained by the use of an oscillating bed, provided that this is

89. Linton, R. R.; Morrison, P. J.; Ulfelder, H., and Libby, A. L.: Therapeutic Venous Occlusion: Its Effect on the Arterial Inflow to an Extremity, as Measured by Means of the Rein Thermostromuhr, Am. Heart J. **21**:721 (June) 1941.

90. Horton, B. T.; Krusen, F. H., and Sheard, C.: An Evaluation of Methods and Mechanical Devices Used in the Treatment of Peripheral Vascular Diseases, Arch. Phys. Therapy **22**:389 (July) 1941.

used in an environmental temperature of 85 to 87 F. (29.5 to 30.5 C.), at which level vasospasm ceases to exist. It must be remembered that this evaluation depended solely on the assumption that surface temperature is an index of blood supply.

A similar evaluation of the usefulness of various physical measures in the treatment of peripheral vascular diseases was presented by Wright.[91] Practically all of the therapeutic agents employed at present are mentioned, with particular emphasis on their indications and contraindications. No specific data are given on the results obtained, but favorable comment is made on agents producing heat, active vascular exercises, the oscillating bed and iontophoresis employing acetylbetamethylcholine. Wright was not convinced of the value of intermittent venous occlusion and, to a lesser degree, the pressure suction boot.

The vasodilating action of a number of procedures used in the treatment of peripheral vascular diseases was investigated by Abramson, Zazeela and Schkloven [92] by means of the venous occlusion plethysmograph. Studies were done on a series of normal patients, patients with peripheral circulatory disease and patients with various mental states. A single administration of calcium gluconate; a deproteinated pancreatic extract (padutin); papaverine hydrochloride; a mixture of atropine, hydrochlorides of opium alkaloids and papaverine (spasmalgin), and thiamine hydrochloride produces only a slight increase or none at all in the blood flow to the hand, the forearm, the leg and the foot. Alcohol, diethylstilbestrol and histamine acid phosphate generally increase the blood flow to the hand but not to any other portion of the extremities. Hypertonic solution of sodium chloride produces an augmentation of the flow to the hand, leg and foot in a third of the trials. The application of a venous occlusion pressure for two or three hours does not produce a significant increase in peripheral blood flow. The authors also presented evidence by their method of study that results of surface temperature studies and oscillometric readings do not necessarily reflect or parallel changes in total blood flow to an extremity. It is our opinion that the data obtained in these experiments are parallel in part to the clinical results obtained from the use of these procedures. This paper also serves to emphasize the need for more thorough investigation of new therapeutic procedures before they are accepted.

Interest is being aroused on the question of heat versus cold in the treatment of certain types of peripheral vascular diseases. The

91. Wright, I. S.: Physical Measures in the Treatment of Peripheral Vascular Disease, J. Mt. Sinai Hosp. **8**:1128 (Jan.-Feb.) 1942.

92. Abramson, D. I.; Zazeela, H., and Schkloven, N.: The Vasodilating Action of Various Therapeutic Procedures Which Are Used in the Treatment of Peripheral Vascular Disease, Am. Heart J. **21**:756 (June) 1941.

previously reviewed work by Allen and his associates on the use of refrigeration as a preliminary to amputation in older patients appears to be gaining favor. Its use in younger persons has recently been suggested by Ochsner,[93] especially in those in whom there is interference with the blood supply as a result of trauma. He suggested that the associated vasospasm be controlled by injection of the sympathetic ganglions with procaine hydrochloride or alcohol. To us the question is not entirely one of controlling the associated vasospasm. It is doubtful if blocking the ganglions will prevent the local action of cold on the vessels anyway. The question is, does collateral circulation develop with the correct amount of refrigeration in these patients or does the cold produce an unchanging condition in the extremity in which neither gangrene nor collateral circulation develops? Many of the details of this form of therapy remain obscure, and consequently more investigation is needed before adoption.

Stein and Weinstein [94] studied the effect of carbon dioxide baths on the peripheral circulation. European authors previously demonstrated that carbon dioxide diffuses through the dermal layers, thus coming into contact with the network of small blood vessels and causing them to dilate. The resultant hyperemia is usually localized to the contact area and is unaccompanied by an appreciable rise in tissue or general metabolism. The authors studied a series of patients submitted to these baths. In all of the subjects the cutaneous temperature increased during the treatment and decreased gradually afterward. When tap water was substituted, the results were similar except that the temperature of the skin fell more rapidly after the completion of the treatment. Capillary studies and blood flow measurements were also made. Blood flow was increased, and in the capillary studies an extraordinarily large number of capillary tufts and loops became visible after exposure. The authors suggest the clinical application of this process but do not report any of their results. One wonders if this is an attempt to resurrect the spa treatments of continental Europe.

Fatherree and Hurst [95] report their observations at Soap Lake, Wash., recently popularized as a spa beneficial to patients with thromboangiitis obliterans. A statistical analysis of 32 patients was made, including not only the usual data but the progress of the disease before and during residence in this area. The apparent popularity of Soap

93. Ochsner, A.: The Use of Refrigeration Combined with Vasodilatation to Preserve Vitality in a Relatively Ischemic Extremity, Surgery **11**:819 (May) 1942.

94. Stein, I. D., and Weinstein, I.: The Value of Carbon Dioxide Baths in the Treatment of Peripheral Vascular Disease and Allied Conditions, Am. Heart J. **23**:349 (March) 1942.

95. Fatherree, T. J., and Hurst, C.: The Spa Treatment of Thromboangiitis Obliterans, Am. Heart J. **22**:180 (Aug.) 1941.

Lake lies in the considerable percentage of gangrenous and ulcerative lesions which heal while the patients are treating themselves in this lake. The authors are of the opinion that the frequent healing of these lesions was not due to the water but occurred because the gangrenous extremities were kept at rest, kept clean and not subjected to meddlesome surgical procedures.

The dietary history and clinical data for 21 patients with Raynaud's syndrome are reported by Spiegel.[96] In most patients the history revealed a deficient intake of vitamins, and in a few clinical avitaminosis was present. These patients were treated for six weeks to one year either with "total vitamins" or with vitamin B complex. Fifteen showed distinct relief from attacks of vascular spasm. Three remained asymptomatic and are being maintained on a normal diet. The vitamin B complex appears to be the effective therapeutic group of vitamins. The authors were unable to determine which was the essential specific factor. When thiamine hydrochloride and pyridoxine were used individually they were ineffective. Thiamine hydrochloride and pyridoxine in large doses actually caused exacerbation of symptoms in patients who had previously improved under vitamin B therapy. Apparently the several components of the vitamin B complex are necessary, although no relation between this deficiency and the pathologic mechanism of Raynaud's syndrome could be adequately explained.

King[97] successfully treated 10 patients with thromboangiitis obliterans with deproteinated pancreatic extract. In all cases relief from intermittent claudication and pain at rest was noted. The subjects studied probably had arteriosclerosis obliterans rather than thromboangiitis obliterans.

Davidson[98] successfully treated 3 patients with septic thrombophlebitis with heparin and sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole). The usual dose of each drug was used.

ABNORMALITIES OF BLOOD PRESSURE

Kean[99] studied blood pressure in West Indians and Panamanians in an effect to add to the information regarding the relation of race and climate to variations in blood pressure. He discusses observations made in many previous reports, some of which are controversial. It has been believed that blood pressure in persons living in the tropics

96. Spiegel, R.: Vitamin Therapy in Raynaud's Disease, J. Mt. Sinai Hosp. **8**:284 (Nov.-Dec.) 1941.

97. King, G. S.: Deproteinated Pancreatic Acid: Use in Thromboangiitis Obliterans, Indust. Med. **10**:530 (Dec.) 1941.

98. Davidson, H. S.: The Treatment of Septic Thrombophlebitis with Heparin and Sulfathiazole, J. M. Soc. New Jersey **38**:642 (Dec.) 1941.

99. Kean, B. H.: Blood Pressure Studies on West Indians and Panamanians Living on the Isthmus of Panama, Arch. Int. Med. **68**:466 (Sept.) 1941.

is low and that hypertension is not common among them. It is said to be rare among the Chinese and in Australian aborigines. The incidence in American Negroes is high, while blood pressure in Negroes living under primitive conditions in Africa is cited as being similar to that in white persons up to the age of 40 and after ths age averaging less than that in white persons.

Kean's own studies were conducted on native Panamanians and West Indians living on the Isthmus of Panama. The incidence of increased blood pressure was much greater in the West Indians than in the native Panamanians. The converse was true for low blood pressure. The average of blood pressures taken was higher for the West Indian group, and the incidence of hypertension was actually greater in this group as well.

It would be of considerable interest to follow up this work with blood pressure studies on West Indians in their home environment. The impression is prevalent that the existence of hypertension and vascular diseases in general is high in the American Negro population. This is quite in contrast to observations made on aboriginal Negroes. To speculate on the factors causing this is, of course, futile, but the question of the effect of change of environment to a cold climate on a vascular system adjusted through generations of life in the tropics is interesting and perhaps important. This may be the reason for the supposed inferior vascular system of the American Negro.

Cold Pressor Phenomena.—The fact that the cold pressor phenomenon in hypertension is dependent on intact peripheral sensation was demonstrated by observations made by Sullivan [100] on a patient with a transection syndrome of fourteen years' duration. The spinal cord had been removed below the level of the first lumbar segment, with complete motor and sensory paralysis. The circulation of the blood in the legs was unimpaired.

When either hand was immersed in ice water a constant rise in blood pressure was noted, from 120 to 140 systolic and from 90 to 104 diastolic on one occasion. An increase in heart rate accompanied this rise in pressure. When a foot was immersed, no constant change was noted either in systolic or in diastolic pressure. This observation substantiates the assumption that the cold pressor response is due to a reflex, resulting from sudden stimulation of the cutaneous nerve endings for pain and temperature sense.

Feldt and Wenstrand [101] have made a comparison of the results of the cold pressor test and the breath-holding test as a stimulus for the

100. Sullivan, J. D.: Dependence of Cold Pressor Reaction on Peripheral Sensation, J. A. M. A. **117**:1090 (Sept. 27) 1941.

101. Feldt, R. H., and Wenstrand, E. E. W.: The Cold Pressor and Breath Holding Test: An Analysis of Results in Two Hundred Subjects, Arch. Int. Med. **67**:1157 (June) 1941.

detection of persons who respond with an excessive rise in blood pressure. Both tests were made on 200 persons with normal and with elevated pressure.

Both procedures were found to produce a rise in blood pressure. Statistically, the response was similar except in one classification. Among normal hyporeactors to the two tests the systolic response to the breath-holding test greatly exceeded the response to the cold pressor test. In most of the subjects the response to the cold pressor test was the same or higher than the response to breath holding. Wide differences were sometimes encountered in the same person. Hyperreaction to cold was observed in 39 persons who reacted normally to breath holding, while in 16 persons the opposite was noted.

While the arithmetical mean results correspond well, the individual differences seem to be too great to indicate that the results can be regarded as showing "striking simularity."

Abramson and Fierst [14] have made observations on blood flow in the forearm, the leg and the hand in hypertensive subjects at rest. Blood flow in the forearm and in the leg was found to be considerably higher in hypertensive subjects than in normal persons. In the hand, on the contrary, blood flow was found to be uniformly less in the hypertensive subjects than in the normal ones, in striking contrast to the results obtained in the forearm and the leg.

When the blood flow was correlated with the height of the blood pressure, it was observed that there was a marked relation between the forearm flow and both systolic and diastolic levels.

From their data the authors conclude that the theory of general and uniformly increased peripheral resistance to blood flow in hypertensive persons cannot be held in view of their observations that blood flow is not the same throughout the body. If the increased resistence is localized, then it might be expected that a more rapid rate of flow would exist in those parts of the body in which the resistance was not increased.

There is, of course, considerable variation of opinion in this respect, and as the authors point out, it cannot be stated that the augmented blood flow through the leg and the forearm is the result solely of an increase in tone of the vascular bed in other parts. Further studies will be necessary to decide this matter ultimately.

The relation of pregnancy and toxemias of pregnancy to later hypertension in women has been the subject of several papers.

A follow-up study [102] of 167 eclamptic women was made. In 147 survivors the incidence of subsequent hypertension was 17.5 per cent.

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102. Chesley, L. C., and Somers, W. H.: Eclampsia and Post Eclamptic Hypertension: Follow Up Study with Analysis of Factors Effecting Remote Prognosis, Surg., Gynec. & Obst. **72**:872 (May) 1941.

Proteinuria occurred in 2.6 per cent. Renal function as usually measured was within the normal range in 97 per cent. The majority had changes in the fundi of significant type, and one half of them had cardiac enlargement. Hypertension was more likely if there had been antecedent renal disease, elevated blood pressure during pregnancy, many previous children or long and severe eclampsia.

Williams, Nix and Manzy [103] in a follow-up study of 224 women with toxemia of pregnancy found that 80 per cent of those above 35 years of age had blood pressures in excess of 140 systolic and 90 diastolic. The severity and the type of toxemia seemed to have no special relation in those who did not have previous hypertension or nephritis. Later hypertension was much more frequent in those who had had toxemia and subsequently had a later pregnancy than in those who had only one pregnancy.

In another statistical study on the subject Isenhour, Kuder and Dill [104] found that the incidence of hypertension both in parous and in nulliparous women was above the average usually stated as normal for men. They believe that it is reasonable to suppose that the vascular system of the female has an increased tendency toward hypertension. This does not seem to be actually demonstrable.

They conclude that there is no relation between hypertension and pregnancy itself and that hypertension and "hypertension-producing" diseases which occur after a large proportion of toxemias of pregnancy are due to defects in the vascular systems of the persons affected which predispose them to both the toxemias of pregnancy and hypertension.

It is apparent that while there is some disagreement in detail, still there is a definite increased frequency of hypertension following this complication of pregnancy, whether it bears a causal relation or whether both conditions have a common underlying cause.

The exact nature of experimental hypertension produced by constriction of the renal artery or by compression of the kidney itself is still under discussion. The similarities to and differences from hypertension in human beings have brought forth efforts both clinical and experimental to link the two forms together and thus place essential hypertension in the classification of renal diseases. Certainly it must be admitted that the numerous counterparts of experimental hypertension encountered in human beings furnish evidence enough to warrant careful investigation of every clinical case showing the symptom com-

103. Williams, T. J.; Nix, H. G., and Manzy, C. H.: The Incidence of Hypertension After the Toxemias of Pregnancy, Am. J. Obst. & Gynec. **42**:98 (July) 1941.

104. Isenhour, C. E.; Kuder, K., and Dill, L. V.: The Effect of Parity on the Average Blood Pressure and on the Incidence of Hypertension, Am. J. M. Sc. **203**:333 (March) 1942.

plex of hypertension. Certainly the separation and grouping of cases showing increased blood pressure is important for no other reasons than those of prognosis and diagnosis, and therefore treatment in some cases.

Schroeder and Steele [105] have continued their clinical studies on hypertension and point out that the identity of essential hypertension has been seriously called into question. They note that chronic bilateral pyelonephritis is now recognized as a cause for the rise in pressure and have therefore investigated a number of other renal abnormalities which they consider to have some significance in this respect.

They studied 250 cases for the purpose of discovering some associated renal disease. Some type of renal disease was encountered in 113. The onset of such disease often occurs much earlier than the development of hypertension, and while the disease itself may be one not usually associated with it, yet the frequency with which renal disease occurs suggests that it may be at least a factor in the genesis of hypertension. Another, according to the authors, may be an inherited predisposition shown in the quality of the vascular system which is responsible for the cold pressor reaction.

Prinzmetal, Hiatt and Tragerman [106] report a case of bilateral infarction of the renal arteries which appeared at autopsy to produce bilateral obstruction of these arteries exactly similar to that produced experimentally by Goldblatt. There was a well marked rise in blood pressure within a few days. The case is a perfect example of acute renal ischemia in a human being. Perfusates of the kidney had the same hypertensive properties as do those of experimental animals. Hypertension following thrombosis of the renal veins has also been reported.[107]

Braasch and Wood [108] encountered 3 instances of hypertension in a group of 70 cases of perinephritis or perinephritic abscess. In these instances it was impossible for the authors to draw any conclusion as to a causal relation to constriction or compression of the kidney.

Baggenstoss and Barker [109] studied a group of cases of unilateral renal atrophy and observed that hypertension was somewhat more fre-

105. Schroeder, H. A., and Steele, J. M.: Studies on "Essential" Hypertension: II. The Association of Hypertension with Organic Renal Disease, Arch. Int. Med. **68**:261 (Aug.) 1941.

106. Prinzmetal, M.; Hiatt, N., and Tragerman, L.: Hypertension in Patient with Bilateral Renal Infarction: Clinical Confirmation of Experiments in Animals, J. A. M. A. **118**:44 (Jan. 3) 1942.

107. Perry, C. B., and Taylor, A. L.: Hypertension Following Thrombosis of Renal Veins, J. Path. & Bact. **51**:369 (Nov.) 1940.

108. Braasch, W. F., and Wood, W. W., Jr.: Clinical Perinephritis and Blood Pressure, Proc. Staff Meet., Mayo Clin. **52**:54 (Jan. 28) 1942.

109. Baggenstoss, A. H., and Barker, N. W.: Unilateral Renal Atrophy Associated with Hypertension, Proc. Staff Meet., Mayo Clin. **16**:833 (Dec. 31) 1941.

quent in their group than could be expected had it occurred only by chance. Increased blood pressure is more likely to be associated if the degree of atrophy is severe. The causes of atrophy were pyelonephritis and hydronephrosis in most instances.

In confirmation of the present state of awareness of the relation between hypertension and renal disease are the large number of individual case reports and extended studies of unilateral renal disease of urologic type in which hypertension is considered a relevant factor.

Reports on cases of juvenile hypertension are increasing in number doubtless because blood pressure observations are now being made on children much more frequently than in years past. Killian and Calvin [110] reported 6 cases of persistent hypertension in children from 4½ to 14 years of age. The hypertension was of renal origin in all cases in only 1 of which the renal disorder was subacute glomerulonephritis. Pyelonephritis, hydronephrosis and congenital unilateral hypoplasia of the kidney made up the balance. The authors note that hypertension may occur much more frequently in childhood than is often suspected.

Powers and Murray [111] have reported 1 case of juvenile hypertension due to pyelonephritis and aplasia of one kidney successfully treated by surgical intervention and have reviewed 14 cases previously reported. The renal lesions in these cases have been classified as neoplastic, obstructive, congenital and inflammatory.

Kimmel's [112] findings in regard to pyelonephritis reflect much the same viewpoint.

Benjamin and Ratner,[113] Court,[114] Toulson and Wagner [115] and Kerley and Lorenze [116] likewise report hypertension in infancy and childhood, in all instances either due to or associated with renal disease, most often pyelonephritis.

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110. Killian, S. T., and Calvin, J. K.: Renal Hypertension in Children, Am. J. Dis. Child. **62**:1242 (Dec.) 1941.

111. Powers, J. H., and Murray, M. F.: Juvenile Hypertension Associated with Unilateral Lesions of the Upper Urinary Tract, J. A. M. A. **118**:600 (Feb. 21) 1942.

112. Kimmel, G. C.: Hypertension and Pyelonephritis of Children, Am. J. Dis. Child. **63**:60 (Jan.) 1942.

113. Benjamin, B., and Ratner, M.: Hypertension Associated with Unilateral Chronic Atrophic Pyelonephritis, Am. J. Dis. Child. **61**:1051 (May) 1941.

114. Court, D.: Malignant Hypertension in Childhood, Arch. Dis. Childhood **16**:132 (June) 1941.

115. Toulson, W. H., and Wagner, J. A.: Congenital Encapsulated Multiocular Serous Cyst of the Kidney Associated with Hypertension: Occurrence in a Nineteen Months Old Infant; Report of Case, Bull. School Med. Univ. Maryland **26**:177 (Jan.) 1942.

116. Kerley, C. G., and Lorenze, E. J.: Blood Pressure Observations on Children in Private Practice, J. Pediat. **20**:383 (March) 1942.

ENDOCRINE HYPERTENSION

The syndrome presented by tumors of the adrenal medulla has been reviewed in previous years. Additional case reports [117] appear frequently, and this disorder is apparently discovered often enough in an early stage to admit to successful surgical treatment.

Hantschmann [118] has, however, reported 5 cases of tumor involving the adrenal cortex associated with hypertension. In 4 of these biopsy or necropsy was done. In 3 cases the patients were women of middle age who showed hirsutism, facial rubor and reduced carbohydrate tolerance in addition to high blood pressure. Of the patients in the other 2 cases, both men, 1 had a hypernephroma and the other a cortical adenoma. Hantschmann believes the rise in blood pressure in these cases to be due to the secretion of a substance which is not epinephrine but related to it. In his opinion this substance has the ability to constrict the arterioles, but no capillary constriction occurs; hence the rubor. The symptoms are somewhat similar to those observed in adenomas of the anterior lobe of the pituitary. Further observations are clearly necessary to evaluate his data.

That chorionepithelioma may be accompanied by hypertension is shown by the reports of Adams.[119]

EXPERIMENTAL HYPERTENSION

Page [120] has reviewed the status of experimental hypertension and presented the views which his extensive work on the subject permit him to form in regard to hypertension in human beings. As is well known, he places the emphasis on the theory of a humoral mechanism for the origin of the disorder and places the location of the effect in the afferent glomerular arteriole, although the essential alteration in the hemodynamics of the renal blood flow lies in the constriction of the efferent glomerular arteriole. He suggests that the process which

117. Crane, J. J.; Alesen, L. A., and Touriel, E. L.: Tumor of the Suprarenal Medulla Associated with Paroxysmal Hypertension: Report of Case Preoperatively Diagnosed and Cured by Surgical Removal, J. Urol. **46**:100 (Dec.) 1941. Hamilton, J. E.: Pheochromocytoma of Adrenal with Paroxysmal Hypertension: Case Relieved by Surgery, Kentucky M. J. **38**:572 (Dec.) 1940. Allen, P. L.: Chromaffic Cell Tumor Associated with Paroxysmal Hypertension, Texas State J. Med. **36**: 640 (Dec.) 1940.

118. Hantschmann, L.: Adrenal Cortex Tumors and Hypertension, Klin. Wchnschr. **20**:377 (April 19) 1941.

119. Adams, J. E.: A Study of Malignant Testicular Tumors Including Case Reports of Chorionephithelioma Accompanied by Hypertension, J. Urol. **47**:491 (April) 1942.

120. Page, I. H.: The Nature of Clinical and Experimental Arterial Hypertension, J. Mt. Sinai Hosp. **8**:3 (May-June) 1941; Arterial Hypertension, J. Urol. **46**:807 (Nov.) 1941.

initiates the disturbance in blood flow is probably arteriosclerosis, which may exist in this portion of the renal vascular structure alone. He discounts the effect of the central nervous system in the genesis of vascular hypertension and explains the results obtained by surgical extirpation of the sympathetic mechanism on the pooling of blood within the splanchic vessels and diminished venous return to the heart which is most evident in the upright posture. Cardiac output is thus limited, and the peripheral pressure remains at a lower level as a consequence. So it may be said, if this is true, that such an operation does not alter the fundamental mechanism which is responsible for the genesis of the disorder in human beings.

The work of Corcoran and Page [121] on renal blood flow in experimental hypertension is comparable to that of other investigators. Renal blood flow is decreased in animals made hypertensive by compression of a renal artery if this compression has been marked or severe. These studies of Corcoran and Page were made on animals who were made hypertensive by only limited compression. Measurements of the renal blood flow calculated from the clearance of phenolsulfonphthalein and of inulin indicated that hypertension did exist without impairment of renal blood flow. Thus, renal ischemia is not essential to production of experimental hypertension. The essential mechanism is said to be intrarenal reduction of pulse pressure. That is, hypertension develops, or the humoral agent responsible for its development is released, as a consequence of the absence of pulsatile blood flow. Renal ischemia when present is then only an accompanying phenomenon. If this is true, the authors reason that the production of renin "must arise in some site normally exposed to high pulse pressure." Such a site must be proximal to the glomerulus and in close relation to the afferent arteriole. Surrounding or adjacent to these structures are groups of cells the nature or function of which is not well known. Because these cells are hypertrophied and show an increase in the number of their granules in animals with experimental hypertension, it has been assumed that they may be the site of the formation of renin.

In this paper a complete review of the subject of renal hemodynamics is discussed and developed in the logical fashion of the authors.

That sympathectomy, even the complete denervation operation of Smithwick, has no effect on renal blood flow as measured by the usual clearance methods was shown in 2 cases by Corcoran and Page.[122] The efferent arteriolar constriction was not reduced in either case studied. These observations corroborate ones made on animals with experimental hypertension. The authors repeat their view in regard

121. Corcoran, A. C., and Page, I. H.: Renal Blood Flow in Experimental Renal Hypertension, Am. J. Physiol. **135**:361 (Jan.) 1942.

122. Corcoran, A. C., and Page, I. H.: Renal Aspects of Experimental and Clinical Hypertension, J. Lab. & Clin. Med. **26**:1713 (Aug.) 1941.

to the effect of sympathectomy being largely due to diminished cardiac output but suggest that the reduction of pressure in a hypertensive patient subjected to the operation may arrest the progress of renal arteriosclerosis and state:

> Since these arteriolar lesions may contribute to the release of renin and the activity of the renal vasopressor system, sympathectomy may thus interrupt for a time the progress of the disease.

This would seem to be a compromise statement, which leaves the reader somewhat doubtful.

Friedman, Selzer and Rosenblum[123] are in essential agreement with Page in regard to the relation of renal ischemia to experimental hypertension. They likewise have found that it is not necessary for the initiation or maintenance of experimental hypertension.

Their observations were made on a group of hypertensive patients showing the disorder in varying grades of severity. They employed the usual clearance methods used for this purpose, including diodrast and inulin clearance. They found that in the majority of patients with hypertension effective renal blood flow was reduced somewhat, although glomerular filtration was approximately normal. The degree of elevation of diastolic pressure did have a direct bearing on the rate of blood flow and the glomerular filtration rate. It is interesting to note that observations on the group who showed intermittent or variable hypertension demonstrated that effective renal blood flow was normal in 2 patients who at the times of observation had normal diastolic blood pressures, but that in 2 others whose diastolic levels were only slightly elevated the flow was reduced.

They noted the increased tonus in the efferent glomerular arteriole and suggest that this represents

> . . . the reflex or chemically motivated ability of these vessels to maintain an effective glomerular filtration pressure despite extra glomerular or intra glomerular hemodynamic changes, whether these changes were of pulse pressure or of blood flow.

The further suggestion is made that the efferent arteriolar constriction in itself initiates renal ischemia.

These observations are in essential agreement with those of Goldring, Chasis, Ranges and Smith,[124] who studied the same procedures in 60 cases of hypertension. They believe that the renal ischemia which is actually demonstrable, that is, constriction of the efferent arteriole of the glomerulus, is a sequel to the mechanism which initiates the hypertensive process. There is no evidence in their observations that renal

123. Friedman, M.; Selzer, A., and Rosenblum, H.: The Renal Blood Flow in Hypertension, J. A. M. A. **117**:92 (July 12) 1941.

124. Goldring, W.; Chasis, H.; Ranges, H. A., and Smith, H. W.: Effective Renal Blood Flow in Subject with Essential Hypertension, J. Clin. Investigation **20**:637 (Nov.) 1941.

ischemia can be regarded as the cause of essential hypertension. Certainly renal ischemia can initiate the mechanism of hypertension, but whether the secondary ischemia (as they regard it) associated with hypertonus of the efferent glomerular arteriole adds to the progress of the disease or is merely the result of some other initiating mechanism remains unanswered.

They are also of the opinion that as a result of the hypotonus of the efferent glomerular arteriole there is progressive impairment of tubular function which progresses at different rates in different persons. In some subjects this tubular impairment seems to exceed impairment of glomerular function.

Certainly there seems to be profound impairment of tubular function and ultimately destruction, which appears to be the essential characteristic of the kidney of hypertension, inasmuch as most observers using these methods are in agreement. The suggested possibility for error lies in the interpretations placed on the results obtained by these methods.

Chasis and Redish [125] found that the process of tubular impairment progresses at the same rate in both kidneys of patients with essential hypertension when impairment is measured according to blood flow. The disturbance in blood flow and filtration rate is exactly the same. They found no evidence of unilateral ischemia.

Wilkins and Duncan [126] studied the effects of angiotonin in normal human subjects by intravenous infusion. Arterial hypertension can thus be produced and controlled by regulating the rate of administration. This hypertension is accompanied by increase in cardiac size and decrease in cardiac output. There is a bradycardia, which the authors regard as vagal in origin. There are an increase in venous pressure, a decrease in vital capacity and an increase in circulation time. There were no significant electrocardiographic changes. There seemed to be some decrease in blood flow in the extremities. The patients experienced some nausea, headache, substernal oppression and palpitation.

All of the effects disappear within a few minutes when administration is stopped. If the substance is injected intradermally, local blanching of the skin is said to occur.

Abell and Page [33] have also studied the effects of angiotonin, renin and other pressor substances on the blood vessels and compared the effects. These observations were made in transparent chambers in rabbit's ears. The results may be summarized as follows: Both renin and

125. Chasis, H., and Redish, J.: Effective Renal Blood Flow in the Separate Kidneys of Subjects with Essential Hypertension, J. Clin. Investigation **20**:655 (Nov.) 1941.

126. Wilkins, R. W., and Duncan, C. N.: The Nature of the Arterial Hypertension Produced in Normal Subjects by the Administration of Angiotonin, J. Clin. Investigation **20**:721 (Nov.) 1941.

angiotonin in small doses cause constriction of the arterioles. The capillaries are not affected, and the venules show but little evidence of constriction. The blood flow is not reduced under ordinary dosage. Parahydroxyphenylethylamine and methylguanidine sulfate act in the same general way.

Equivalent amounts of epinephrine and pitressin result in extreme vasoconstriction of the arterioles. The constriction endures for a much longer time, and the peripheral blood flow is markedly reduced or abolished entirely. The venules also show a much more marked reaction, and the capillaries are not affected at all.

Thus by direct observation it is noted that angiotonin and renin react in the manner postulated to fulfil the requirements for the hypertensive mechanism. That is, they elevate blood pressure by moderate arteriolar constriction but have no effect in reducing blood flow. The force of the heart beat is also increased. Parahydroxyphenylethylamine and methylguanidine act in a similar manner, but epinephrine and pitressin produce such extreme arteriolar constriction that blood flow is impeded.

Landis [127] observed the effects of heat-treated extracts of the kidneys obtained at autopsy from 16 persons with normal blood pressure and 34 with well marked hypertension. Extracts from patients with benign hypertension and chronic glomerulonephritis used in the assay on anesthetized nephrectomized rabbits were without greater effect than those from patients with normal blood pressure. The extracts prepared from 4 patients with malignant hypertension all showed an augmented pressor activity but with a variation in activity which was so great that definite conclusions could not be drawn. Pressor substances were obtained from all kidneys studied.

The pressor mechanism responsible for experimental hypertension, and probably for the clinical type, consists in the production by the kidney of increased amounts of renin. In the circulating blood this is altered by the renin activator, which is produced in the liver.[128] Angiotonin, the actual pressor substance is thus produced. If the renin activator is not manufactured by the liver in adequate quantity as a result of hepatic damage or by hypatectomy, blood pressure at the higher levels is no longer maintained. Animals in which the liver has been damaged or removed respond to injected angiotonin as before but not to renin alone.

The question as to whether the vascular mechanism in hypertension is abnormally sensitive to normal amounts of pressor substance (angio-

127. Landis, E. M.: Hypertension and the Pressor Activity of Heated Extracts of Human Kidneys, Am. J. M. Sc. **202**:14 (July) 1941.

128. Page, I. H.; McSwain, B.; Knapp, G. M., and Andrus, W. deW.: The Origin of Renin-Activator, Am. J. Physiol. **135**:214 (Dec.) 1941.

tonin) has been answered in the negative, as far as experimental hypertension is concerned.[129] Dogs with hypertension are no more susceptible to angiotonin than are normal animals. Renin, however, does cause a greater response, and this seems to be the result of increased formation of angiotonin within the animal from the combination of renin and its activator, which is apparently present in increased quantity in the liver of experimental animals.

THE COUNTERPRESSOR MECHANISM

Wakerlin and Johnson[130] have continued their observations on the production of what was thought to be an antiserum for dog renin in the rabbit and for hog renin in the dog. This has been extended to different species. It was found that antirenin could not be produced in homologous animals; that is, antirenin to rabbit renin could not be produced in the rabbit, but only in another species. But the antiserums produced could neutralize the pressor effect of renin from other species as well.

As the result of daily injections of hog renin, the blood pressures of hypertensive dogs fell strikingly. Heat-inactivated hog renin and active dog renin were without effect. The serums of the dogs treated with hog renin only neutralized the pressor effects of renin. Daily intramuscular injections given similarly to dogs with normal blood pressure seemed to prevent the development of hypertension when these animals were subsequently operated on. The authors do not attempt to explain these actions but suggest the development of an antihormone.

Certainly it is impossible to make any estimate of the significance of these observations.

Page and his co-workers[131] have continued their observations of blood pressure–reducing extracts obtained from kidneys. There can be no doubt as to the presence of these substances, but so far their identity is not known, and the use of the extracts which the authors have obtained still yields occasional shocklike reactions. It is also still not possible to secure uniform preparations of high potency. The report alluded to here refers to observations on 280 hypertensive dogs, 13 patients with malignant hypertension and 6 patients with hypertension in the so-called benign phase.

129. Page, I. H.: The Pressor Response of Normal and Hypertensive Dogs to Renin and Angiotonin, Am. J. Physiol. **134**:789 (Nov.) 1941.

130. Wakerlin, G. E., and Johnson, C. A.: Effect of Renin on Experimental Renal Hypertension in the Dog, J. A. M. A. **117**:416 (Aug. 9) 1941.

131. Page, I. H.; Helmer, O. M.; Kohlstaedt, K. G.; Kempf, G. F.; Gambill, W. D., and Taylor, R. D.: The Blood Pressure Reducing Property of Extracts of Kidneys in Hypertensive Patients and Animals, Ann. Int. Med. **14**:347 (Sept.) 1941.

Similar results in the reduction of blood pressure of rats made hypertensive have been reported by Jensen and his associates.[132] They were able by the use of renal extracts to reduce the blood pressure in their experimental animals significantly.

MEDICAL THERAPY OF HYPERTENSION

Except for the experimental use of kidney extracts and improvements in surgical management there have been no advances in the management of hypertension with the possible exception of the use of vitamin A. No evaluation of this method has as yet been made.

Govea Pena and Villaverde[133] have treated 65 patients. Massive doses of vitamin A were used, as much as 180,000 international units daily. Within a few days lowering of pressure amounting to 30-50 mm. of mercury was noted. The dose was then reduced 50 per cent and continued for longer periods. The authors report prompt relief of the clinical symptoms, such as headache and vertigo. There were 4 patients with hypertension of the malignant type in the group, and they did not show any improvement. The authors recommend the administration of vitamin A by mouth.

The use of thiocyanate drugs has apparently increased. Barker, Lindberg and Wald[134] have an additional communication on the subject. Their results are about as previously reported, with nearly 50 per cent of patients significantly benefited when the concentration of these drugs in the blood was maintained within the effective range of 8-12 mg. per hundred cubic centimeters. Improvement usually occurred in two to four weeks, but sometimes three months of therapy was required. They emphasize that doses must be individualized to meet the needs of each patient.

There were no deaths from toxic reactions, and relatively few patients showed toxic reactions requiring discontinuance of the drug. There were no severe toxic manifestations as long as the blood level was kept below 20 mg. per hundred cubic centimeters. Mild toxic symptoms, fatigue, anemia and dry scaling skin were not uncommon after prolonged therapy.

It is interesting to note that the authors state that in no case in which there was failure of response to thiocyanate therapy did splanchnic

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132. Jensen, H., and others: Reduction of Arterial Blood Pressure of Hypertensive Rats by Administration of Renal Extracts, J. Pharmacol. & Exper. Therap. **73**:38 (Sept.) 1941.

133. Govea Pena, J., and Villaverde, M.: Tratamiento de la hipertension arterial permanente por dosis altas de vitamina A, Rev. cubana de cardiol. **2**:332 (Sept.-Dec.) 1940.

134. Barker, M. H.; Lindberg, H. A., and Wald, M. H.: Experiences with Thiocyanates, J. A. M. A. **117**:1591 (Nov. 8) 1941.

section result successfully, but in such cases thiocyanates administered after surgical intervention produced a satisfactory response. No explanation is offered.

Severe poisoning in experimental animals (40-65 mg. per hundred cubic centimeters of blood) did not result in parenchymal damage except to the liver and bone marrow. It is interesting that these results resembled those reported by Page and associates [128] in their studies on the origin of the renin activator. The renin activator is produced in the liver, and it has been found that when the liver was damaged by carbon tetrachloride and alcohol, the production of renin activator failed.

Most of the recent reports on the use of thiocyanates bear out in detail the views of Barker and associates in regard to toxicity, dangers and effectiveness. In fact, the results reveal an almost startling similarity in percentages of benefit. It would seem that this is the only medical treatment which shows any degree of specificity in results beyond what may be expected from sedative, symptomatic treatment.

Among the papers presented in the past year on the subject the one by Kurtz, Shapiro and Mills [135] is interesting and contains observations which follow closely the results of Barker and co-workers. The first-named authors believe that the dangers of the proper use of potassium thiocyanate when blood levels are controlled weekly are small, but they emphasize that both the patient and the physician must be willing to cooperate fully in the control of the blood levels. Treatment should not be offered to a patient who is unwilling to subject himself to this control. Organic heart disease and even rather marked degrees of renal impairment have not proved to be contraindications in the hands of these investigators.

It is to be noted in this respect that Barker, Lindberg and Wald found that 2 patients with angina pectoris suffered attacks of precordial pain when their blood pressures reached too low a level. Reduction in dose and a restoration of a higher level of blood pressure resulted in relief.

That the contrary is also true can be stated by one of us (G. W. S.) who has seen frequent episodes of precordial pain accompanying periods of elevation of blood pressure. When these higher ranges of pressure were controlled with thiocyanate therapy, the episodes of precordial pain become much less frequent. Apparently, then, there is an optimal level of blood pressure for those patients with hypertension who have extensive visceral, particularly coronary, arteriosclerosis.

Although emphasizing that thiocyanates are only an adjunct to the treatment of hypertension, Hines [136] states that better results than ever

135. Kurtz, C. M.; Shapiro, H. H., and Mills, C. S.: The Results of Sulphocyanate Therapy in Hypertension, Am. J. M. Sc. **202**:378 (Sept.) 1941.

136. Hines, E. A.: The Treatment of Hypertensive Disease, Proc. Staff Meet., Mayo Clin. **17**:184 (March 25) 1942.

before are obtainable today by medical treatment with the controlled use of these drugs. He points out that there is a wide range of individual tolerance to these drugs and marked variation in the rate of elimination. This is in agreement with the observations of other authors, including Blaney, Geiger and Ernst,[137] who made a carefully controlled study of the clinical use of thiocyanates by alternating periods of drug administration with periods during which a placebo was administered. No other treatment was used, and patients continued their daily routine of work, diet and rest, without alteration. The results obtained under this program were similar to those already discussed. About one-half the patients so treated were benefited.

Caviness, Umphlet, Peasley, Bell and Satterfield[138] report similar results for a group of 120 patients.

A CRITICAL REVIEW OF THE LITERATURE ON SURGICAL TREATMENT

BY DR. DE TAKÁTS AND DR. MARCUS

VENOUS THROMBOSIS

A great deal of attention is focused on the early recognition of small, subclinical thrombi. In a significant article Bauer[139] reiterates his previously expressed belief that a floating, femoral thrombus originates in the deep veins of the lower part of the leg and that it can be diagnosed by visualization of the superficial and the deep veins after injection of 35 per cent diodrast. When an early limited area of venous occlusion is discovered, the choice of treatment is heparin, which is administered in intermittent doses of 100 mg. three times a day. Heparin was given until the pulse became normal, usually for three to five days. Of 21 patients treated with nothing else but heparin, all were out of bed in six to eight days after the onset of symptoms. No further extension or embolization took place. Of 32 patients treated with lumbar sympathetic block, heat and elevation, the thrombosis remained localized to the lower portion of the leg in only 25 per cent; a propagation of the thrombus into the femoral vein took place in 75 per cent. In 31 per cent thrombosis became bilateral; in 16 per cent pelvic thrombosis occurred, causing 1 death. Large or small pulmonary infarcts were seen. The average length of stay in bed was forty-three days.

This small but carefully observed series seems to give heparin the first choice in the treatment of ascending thrombosis. Welch and

137. Blaney, L. F.; Geiger, A. J., and Ernst, R. G.: Potassium Thiocyanate in Treatment of Hypertension, Yale J. Biol. & Med. **13**:429 (March) 1941.

138. Caviness, V. S.; Umphlet, T. L.; Peasley, E. D.; Bell, T. A., and Satterfield, G. H.: Potassium Sulfocyanate in Treatment of Hypertension, North Carolina M. J. **2**:275 (June) 1942.

139. Bauer, G.: Venous Thrombosis, Arch. Surg. **43**:462 (Sept.) 1941.

Faxon,[140] who are equally emphatic in emphasizing the value of venograms, distinguish between the inflammatory type of thrombophlebitis and the stagnant, bland phlebothrombosis. In the former type sympathetic block rapidly reduces temperature and edema; in the latter type ligation proximal to the thrombosed segment is recommended because of the danger of pulmonary embolism. In acute superficial phlebitis division of the saphenous vein at the groin is advocated; in deep phlebitis division of the femoral vein is done in all patients above the age of 40, as above this age the danger of embolism is markedly increased. Division of the femoral vein, preferably below the profunda, is indicated at any age if an infarct has already occurred. When infarcts have occurred but the source of thrombosis is not evident, venography is done on both sides, and if thrombosis is detected, ligation of the femoral vein on the corresponding side is undertaken.

Equally active intervention is advocated by Starr, Frank and Fine.[141] They believe in doing venography on both sides as thrombosis of the deep veins is frequently bilateral, and ligation of one femoral vein may be followed by pulmonary embolism from the other side. Fine and Sears[142] advise routine ligation of the femoral vein when thrombosis of the deep veins of the lower portion of the leg is present or suspected. If the profunda and the saphenous vein are open, there is no permanent edema resulting from the ligation of the femoral vein. The authors feel that heparin is too expensive, its use requires a great deal of nursing care and its administration is a burden to elderly patients, who have to be kept immobilized with intravenous drip apparatus.

Enthusiasm for venography is somewhat dampened by a report of Homans[143] on thrombosis as a complication of injection of 50 per cent diodrast. We have observed this ourselves in 2 patients.

It is our impression that careful clinical observations may often reveal the site of thrombosis without venography; if a patient is young, and no infarct has occurred, elevation of the foot of the bed, active motion in bed and small doses of heparin injected intermittently can be tried; if an infarct has occurred, there can be no question about the advisability of a ligation proximal to the thrombus. It is obvious, however, that often a thrombus has already reached the iliofemoral vein by the time a surgeon sees a patient. He has, in that event, the choice of ligating the external or the common iliac vein or aspirating the clot through the

140. Welch, C. E., and Faxon, H. H.: Thrombophlebitis and Pulmonary Embolism, J. A. M. A. **117**:1502 (Nov. 1) 1941.

141. Starr, A.; Frank, H. A., and Fine, J.: The Venographic Diagnosis of Thrombophlebitis of the Lower Extremities, J. A. M. A. **118**:1192 (April 4) 1942.

142. Fine, J., and Sears, J. B.: The Prophylaxis of Pulmonary Embolism by Division of the Femoral Vein, Ann. Surg. **114**:801 (Oct.) 1941.

143. Homans, J.: Thrombosis as a Complication of Venography, J. A. M. A. **119**:136 (May 9) 1942.

femoral vein. The latter method seems far simpler for the patient. Intermittent administration of heparin makes its use less cumbersome and also less expensive than the continuous drip method.[144] The recently advocated dicoumarin 3,3′-methylenebis-4-hydroxycoumarin,[145] inexpensive and orally administered, is still not past the experimental stage. Its daily control by accurate determinations of prothrombin prohibits its use in the home or in the smaller hospital. Its damaging action on the liver is still not above suspicion.

ARTERIAL OCCLUSIONS

The management of acute embolic occlusions of peripheral arteries is discussed by Atlas.[146] He reports 2 cases in which minute emboli lodged in the periphery of the leg and gave rise to bilateral vasospasm of such magnitude that a saddle embolus of the aorta was simulated. In both cases the patients were treated conservatively, and within twenty-four and seventy-four hours, respectively, pulsations returned to the extremities.

The conservative measures employed were: intravenous administration of papaverine, administration of heparin, protection of the limb by an unlighted cradle and wrapping the limb in cotton. After the initial spasm disappears, collateral circulation may be stimulated by mild local heat, rhythmic venous occlusion or suction and pressure therapy. Embolectomy is indicated if conservative measures fail to improve the ischemia.

In 2 other cases resection of thrombosed segments due to periarteritis nodosa produced almost immediate release of the reflex spasm in the collateral bed.

The observations of Atlas on the occurrence of small emboli producing ischemia out of proportion to the extent of organic occlusion are of great clinical interest. Certainly many massive arterial occlusions are preceded by showers of just such emboli, and if they were promptly treated with antispasmodics and anticoagulants further emboli or superimposed thromboses might be avoided.

Individual cases of successful embolectomy, in which early diagnosis and postoperative heparinization were stressed, were reported by Ravdin

144. Crafoord, C., and Jorpes, E.: Heparin as a Prophylactic Against Thrombosis, J. A. M. A. **116**:2831 (June 28) 1941.

145. Bingham, J. B.; Meyer, O. O., and Pohle, F. J.: Studies on Hemorrhagic Agent 3,3′-Methylenebis (4-hydroxycoumarin): Its Effect on Prothrombin and Coagulation Time of Blood of Dogs and Humans, Am. J. M. Sc. **202**:563 (Oct.) 1941.

146. Atlas, L. N.: The Management of Acute Embolic Occlusion of the Arteries to the Extremities, Surg., Gynec. & Obst. **74**:236 (Feb.) 1942.

and Wood [147] and Bancroft and Glick.[148] Pratt [149] reviewed 26 cases of arterial embolism in 12 of which embolectomy was performed, with 5 survivals. He reports 1 remarkable case in detail in which clots were removed from both femoral arteries sixty hours after the onset of a saddle embolus. The left leg recovered, but the right leg had to be amputated.

VASCULAR INJURIES

Mason [150] writes a timely article on the management of vascular injuries. Great improvement has been brought about by the use of blood transfusions when severe hemorrhage is encountered. He classifies most vascular injuries into those which demand immediate treatment and those in which a brief period of delay is permissible. There is finally a third group of those which come under observation at a late period. Traumatic aneurysms should not be operated on before the twelfth day after occurrence; this short delay gives sufficient time for the development of collateral circulation; the injured vessel may heal, and infection is less apt to occur. Occasionally, spontaneous healing may take place. The question of ligation versus suture is discussed in regard to war surgery. The dangers following ligation of large arterial trunks are especially great in an exsanguinated patient. These may be gangrene, trophic disturbances and muscle paralysis. To offset the results of sudden vascular occlusion caused by the ligature, certain mechanical and physiologic measures are available. Of the mechanical means, alternate suction and pressure, intermittent venous hyperemia and use of the Matas compressor are discussed. Preferred to these mechanical devices are the physiologic methods, such as sympathectomy or procaine block of the sympathetic nerves, which give striking improvement of circulation. Of course, arterial suture is always preferable to ligation except when severe infection is present or when ligation can be safely performed without jeopardizing the viability of the distal parts. The postoperative use of heparin has increased the number of favorable results.

For arteriovenous aneurysms of longer standing, quadruple ligation with excision of the sac is recommended because it is easier to do and because there is sufficient collateral circulation. In the earlier cases transvenous arterial suture is the method of choice.

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147. Ravdin, I. S., and Wood, F. C.: The Successful Removal of a Saddle Embolus of the Aorta, Eleven Days After Acute Coronary Occlusion, Ann. Surg. **114**:834 (Nov.) 1941.

148. Bancroft, F. W., and Glick, A. H.: Arterial Embolectomy, Ann. Surg. **114**:1093 (Dec.) 1941.

149. Pratt, G. H.: The Surgical Treatment of Peripheral Embolism, Am. J. Surg. **50**:566 (June) 1942.

150. Mason, J. M.: Treatment of Vascular Injuries, Ann. Surg. **114**:191 (Aug.) 1941.

The principles laid down in this paper are clearly defined and should be widely distributed to all those who may come in contact with war injuries involving large vessels of the extremities. Vascular injuries occur much more frequently during war than during peacetime. Their proper management may result in the saving of limbs and lives. Fractures, more dramatic and more mechanical, often overshadow concomitant impairment of circulation.

ANEURYSMS

Twenty-four cases of aneurysm of the abdominal aorta encountered at the Philadelphia General Hospital in ten years are reported by Eliason and McNamee.[151] In only 10 cases of the series was the aneurysm syphilitic; in the rest it was arteriosclerotic. In none of the cases was trauma an etiologic factor. In only half of the cases was the condition diagnosed correctly. The dominant symptom was pain, but its radiation was rather inconstant. Roentgenograms were made in 16 cases, in 11 of which erosion of vertebrae was evident. A pulsating mass could be felt in slightly over one half of the cases (54.1 per cent). Of the 16 cases in which autopsy was done, in 10 the aneurysm was ruptured, retroperitoneally in 9 and into the jejunum in 1. Of the 8 cases in which necropsy was not done, there was clinical evidence of rupture in 2.

Exploratory laparotomy was done in 7 cases, in 5 of which reparative work was done. In 3 cases the aneurysm was wired; in 1 case the left common iliac artery was ligated for ten days, and in another an arteriovenous anastomosis was attempted between the iliac vessels. Unfortunately, nothing is said about the results in the 5 cases.

From Guy's Hospital in London, Brock[152] reports in detail a case of aneurysm of an innominate artery in which ligation was successful. The operation still remains formidable, but successes obtained amply justify further attempts of surgical therapy.

Transthoracic, transpleural ligation of the first portion of the left subclavian artery is recommended by Touroff[153] for aneurysms or other conditions requiring a proximal ligature. The approach is through the front after-division of the second and the third costal cartilage. After the pleura is entered and the lung permitted to collapse, the first portion of the subclavian or the innominate artery is easily indentified and tied.

There is no danger of injury to the thoracic duct, the brachial plexus or adjacent large vessels at the root of the neck; also removal of portions of the clavicle, the sternum or ribs becomes unnecessary. Surgeons

151. Eliason, E. L., and McNamee, H. G.: Abdominal Aneurysm: A Report of Twenty-Four Cases, Am. J. Surg. **56**:590 (June) 1942.

152. Brock, R. C.: Aneurysm of the Innominate Artery: Report of Case Treated Surgically, Guy's Hosp. Rep. **90**:180, 1940-1941.

153. Touroff, A. S. W.: Transthoracic Transpleural Ligation of the First Portion of the Left Subclavian Artery, Surgery **10**:747 (Nov.) 1941.

who have had to struggle in the past with aneurysms of the subclavian artery in the neck will welcome this approach.

Richards and Learmonth [154] performed a lumbar sympathectomy on the right side in a 30 year old patient, after which the right femoral artery was occluded by digital pressure for five minutes three times a day. The right foot was 11 C. warmer than the left one six days after sympathectomy. With these precautionary measures, an aneurysm of the right popliteal artery was excised, necessitating the ligature of the right popliteal and the right superior, medial and middle genicular arteries. After operation the right foot remained warmer than the left one, and muscle pain or wasting did not develop. The pedal pulses disappeared.

In our experience the combination of preliminary sympathectomy with an excision of an aneurysmal sac, especially in the popliteal region, has been most gratifying. In elderly patients with arteriosclerotic aneurysm a sympathetic block with alcohol will occasionally suffice to bring on spontaneous clotting in the aneurysmal sac.

Wildegans [155] reports 55 cases of traumatic aneurysm. Lately arteriography was employed to map out the extent and pattern of collateral circulation. He reports 7 cases in detail, in which one ligature and three lateral and one circular suture were done. Even in the circular suture he obtained good permeability of the artery.

While such feats are undoubtedly possible, especially with the aid of heparin, ligation and resection with preliminary sympathectomy is undoubtedly the simplest method and the one that is best applicable to the surgery of war.

Gamm [156] reports a case of arteriovenous communication between the anterior tibial artery and vein, which followed the use of a Steinmann pin. The heart did not become enlarged, but pulse pressure and pulse rate were elevated. The oscillometric and temperature readings were higher on the affected side. Operation consisted of tying the vein and lateral suture of the artery. Heparin was given intravenously for forty-eight hours. The pulsation of the dorsalis pedis artery was preserved, which is truly an excellent result.

CAROTID SINUS SYNDROME

Ray and Stewart [157] present 4 cases of hypersensitive carotid sinus reflex of the vagal type, in which the carotid sinus nerve and the

154. Richards, R. B., and Learmonth, J. R.: Lumbar Sympathectomy in the Treatment of Popliteal Aneurysm, Lancet **1**:383 (March 28) 1942.

155. Wildegans, H.: Die Arteriographie bei traumatischen Aneurysmen, Chirurg **13**:6 (Jan.) 1941.

156. Gamm, K. E.: Arteriovenous Fistula, J. A. M. A. **119**:134 (May 9) 1942.

157. Ray, B. S., and Stewart, H. J.: Observations and Surgical Aspects of the Carotid Sinus Reflex in Man, Surgery **11**:910 (June) 1942.

carotid body were removed. The complaints were uniformly those of recurring syncope. In all 4 cases bradycardia and syncope occurred when the carotid sinus was compressed. Pulse rate, blood pressure and electrocardiographic changes were recorded during and after compression, with and without protection with atropine.

On exposure the carotid arteries showed signs of moderate to severe arteriosclerosis with visible atheromatous plaques in the walls. The patients' ages varied between 58 and 68. After the operation there was no return of spontaneous attacks of syncope, and no changes could be induced by pressure on the carotid sinuses. During operation ether did not abolish the reflex response induced by pressure on the carotid sinus. The authors emphasize that the degree of response is in direct proportion to the suddenness and the amount of pressure on the carotid sinus.

They also report a cerebral type of hyperactive carotid sinus reflex, in which cure followed the excision of tuberculous nodes in the neck.

It is well to note that atropine given orally in the vagal type produced tachycardia and the usual unpleasant symptoms but did not protect patients against syncope. The frequent occurrence of local changes in the arteries or adjacent soft tissues on the side from which the hyperactive reflex can be elicited suggests that the abnormal reflex does originate in the sinus. These results, supported also by some of our unpublished observations, suggest that the cerebral, central origin of these reflexes, postulated by some workers, is not substantiated at least for one group of cases.

VASOMOTOR APPARATUS IN PERIPHERAL VASCULAR DISEASE

Van Buskirk [158] studied the recurrent branches of the communicating rami and found that some of them join anterior spinal roots at higher levels than the foramen through which they enter the vertebral canal. Such unmyelinated fibers may ascend as much as six or more segments. Thus an anatomic explanation is afforded for failure to obtain complete sympathetic denervation of the arm by extirpation of the stellate ganglion and the upper two or three thoracic segments of the sympathetic trunk. Fibers originating below the third thoracic segment ascend in the vertebral canal and may join the peripheral nerves of the upper extremity through the intervertebral foramens of the first thoracic and the lower cervical segments. If this work, done on cats, may be applied to human beings, it could explain some of the incomplete denervations or recurrences in upper extremities.

158. van Buskirk, C.: Nerves in the Vertebral Canal: Their Relation to the Sympathetic Innervation of the Upper Extremities, Arch. Surg. **43**:427 (Sept.) 1941.

Kuntz and Dillon [159] found that in experiments on cats and monkeys reflex vasoconstriction of the digits of the upper extremity could be demonstrated after removal of the second and the third thoracic segment of the sympathetic trunk. They concluded that the first thoracic nerve must contain preganglionic fibers going to the upper extremity. If these conditions are present in human beings, complete sympathetic denervation of the upper extremity cannot be accomplished by any surgical procedure which leaves the stellate ganglion with its gray communicating rami intact and which does not interrupt the preganglionic components of the first thoracic nerve.

Because of a technical error in 1 of his cases Atlas [160] was able to observe the effects of the isolated removal of the third dorsal ganglion, whereas, on the other side the white rami of the second ganglion were destroyed. On the side of the incomplete preganglionic section the sympathetic denervation of the arm was incomplete. This is contrary to the experience of Livingston, who stated that removal of the third ganglion results in adequate sympathectomy of the arm. Atlas stresses the importance of removing the third rib posteriorly and identifying the level of segments to be removed.

These three articles are cited to present the still unsolved problem of freeing the upper extremity from vasomotor control. In previous reviews we have cited the contention of White and Smithwick, again expressed in their admirable monograph,[161] that in the upper arm preganglionic section is preferable to the postganglionic one. They have never found any reflex sweating or vasomotor activity after operation and have stressed various methods to prevent regeneration of the cut segments. In addition to their work on patients, the work of Sheehan and Marrazzi [162] may be cited; the last-named authors failed to find any sympathetic fibers in the first thoracic segment of monkeys going to the upper extremity which could be detected by as sensitive a recording mechanism as the cathode ray oscillograph.

Clinically, it all revolves around the problem of resecting or leaving the first thoracic outflow intact. The test case is that of Raynaud's disease, in which most of the sensitizations, recurrences and regenerations

159. Kuntz, A., and Dillon, J. B.: Preganglionic Components of the First Thoracic Nerve: Their Role in the Sympathetic Innervation of the Upper Extremity, Arch. Surg. **44**:772 (April) 1942.

160. Atlas, L. N.: The Role of the Second Thoracic Spinal Segment in the Preganglionic Innervation of the Human Hand—Surgical Implications, Ann. Surg. **114**:456 (Sept.) 1941.

161. White, J. C., and Smithwick, R. H.: The Autonomic Nervous System: Anatomy, Physiology and Surgical Application, ed. 2, New York, The Macmillan Company, 1941.

162. Sheehan, D., and Marrazzi, A. S.: Sympathetic Preganglionic Outflow to Limbs of Monkeys, J. Neurophysiol. **4**:68 (Jan.) 1941.

seem to occur. Personal observations on preganglionic and postganglionic sympathectomies performed on the two extremities of the same patients impress us at present with the superiority of preganglionic section.

Hyndman and Wolkin [48] submit considerable evidence that Raynaud's disease is primarily not a disorder of the sympathetic nervous system but, as contended by Lewis, is a local vascular fault. They attribute the beneficial effect of sympathectomy to the relief from pain due to exposure to cold. They also believe in the existence of afferent, pain-bearing sympathetic fibers, many of which course in the sheaths of major vessels. Their interesting line of thought, documented by careful clinical studies, is recommended for study to those working in this field. They feel that it is necessary only to remove the second thoracic ganglion in order to sympathectomize completely the upper extremity. The trauma incident to the removal of the stellate ganglion may be the reason for better results of the preganglionic section.

Atlas [163] describes a patient suffering from deep, constant, aching pain in an anesthetic area of hand and fingers which followed injury to the median nerve. He feels that the painful and trophic phenomena were caused by vasospasm due to sensitization of the peripheral vessels to epinephrine. The postganglionic fibers to these vessels were cut in the median nerve. A preganglionic sympathectomy gradually relieved the pain and cyanosis.

The interpretation of these results is not easy. Other mechanisms may be suggested for the explanation of the relief from pain. The problem arising here is the same encountered in Sudeck's atrophy, where sympathectomy relieves the pain presumably by washing out or neutralizing the pain substances arising from continuous efferent stimulation of posterior root fibers.

Richter and Woodruff [164] describe a simple and accurate method for mapping out areas which have been sympathectomized. These areas show a high electrical resistance to the passage of a small direct current. The areas of high resistance produced by sympathectomy closely follow the sensory dermatomes. The method can be applied to determine the success of an operation or the presence of regeneration.

We have used such a test several years ago and can fully confirm its accuracy and sensitivity. For practical purposes, however, the warm dry and cold damp areas in a sympathectomized limb can be readily detected by a palpating hand. Streaks of nondenervated segments cer-

163. Atlas, L. N.: Further Observations on the Etiology of Vasomotor Disturbances Following Peripheral Nerve Section, Surgery **10**:318 (Aug.) 1941.

164. Richter, C. P., and Woodruff, P. G.: Changes Produced by Sympathectomy in the Electrical Resistance of the Skin, Surgery **10**:957 (Dec.) 1941.

tainly follow sensory dermatomes. Their presence should be looked for after all sympathectomies.

Traumatic arterial spasm is of increasing importance during war. The use of violent traction methods may precipitate arterial spasm. Cohen [165] feels that complete reduction of fractures may often be postponed for a few days with greater safety. The effects of prolonged vasoconstriction and consecutive ischemia are so serious, especially in potentially or actually infected limbs, that every effort must be made to overcome arterial spasm. Early exploration seems to be the most reliable method to release vasospasm.

Henry [166] presents several cases of comminuted fractures in which peripheral vasospasm may inhibit normal healing. Because of impaired circulation under such circumstances infections are more apt to develop in spite of thorough débridement and therapy with sulfonamide compounds. Lumbar sympathectomy abolishes vascular spasm and creates favorable conditions for control of infection and repair. He advocates the routine use of lumbar sympathectic block in severe trauma to the lower extremities.

Adams-Ray [167] recommends injection of procaine into sympathetic ganglions after frostbite of the extremities. He believes that even after the action of cold has ceased, there remains persistent local ischemia due to vasospasm, which produces painful sensory disturbances. The residual pain may also be due to injury to the local nervous tissue. Protracted and intractable sensory disturbances responded promptly to block of the sympathetic ganglions.

Surgical treatment of the sympathetic nervous system in cases of arteriosclerosis and thromboangiitis obliterans is of no value, according to Pennoyer.[168] When the nutrition of the tissues is impaired, the accumulation of metabolites produces arteriolar and capillary paralysis. This is the explanation of the pallor on elevation and rubor on dependence so commonly observed in such disorders. This metabolite control of circulation eliminates vasomotor control. Patients showing a rise in cutaneous temperature after nerve block offer a favorable prognosis for nonsurgical therapy, as the arterial system is elastic enough to be capable of improvement.

In our experience, removal of the vasomotor tone from a vascular tree with impaired circulation frees it from many repeated stimuli of

165. Cohen, S. M.: Traumatic Arterial Spasm, Guy's Hosp. Rep. **90**:201, 1940-1941.

166. Henry, J. P.: Traumatic Vasospasm and Its Relationship to Wounds of the Lower Extremity, Am. J. Surg. **56**:49 (April) 1942.

167. Adams-Ray, J.: Novocaine Block of the Stellate Ganglion: Therapeutic Aid in Sensory Disturbances Caused by Cold, Acta chir. Scandinav. **85**:1, 1941.

168. Pennoyer, G. P.: Peripheral Arterial Occlusion, Am. J. Surg. **53**:102 (July) 1941.

reflex or central origin and favors the action of conservative measures, which tend to accelerate the development of collateral circulation. This is true of certain types of Buerger's disease and also some forms of arteriosclerosis in which vasospastic claudication develops.[40] Atlas,[169] however, has reported 3 cases of gangrene following lumbar sympathectomy. In all 3 the surface temperature of the feet rose appreciably after the operation, but nevertheless, patchy areas of necrosis appeared between one and two weeks after the operation, necessitating finally amputation through the thigh in all 3 cases.

For many years we have treated certain arteriosclerotic occlusions by blocking sympathetic nerves with alcohol. Improvement and better response to conservative therapy have been occasionally striking. Patients with continuous and intractable pain at rest, however, are often on the verge of gangrene, and the lowering of blood pressure, slowing of circulation, or increase in the coagulability of the blood following operation may well be the straw that breaks the camel's back. The explanation of Atlas, that arteriovenous shunts divert too much blood from the terminal vascular bed and the diversion is not compensated by increased flow from the collateral circulation, is a possibility which deserves further investigation. This report is a valuable warning to those doing sympathectomies for arteriosclerotic occlusion to regard continuous intractable pain at rest an immediate forerunner for gangrene. In fact, we believe that such a symptom defies all efforts at alleviation and indicates amputation.

SURGICAL TREATMENT OF HYPERTENSION

Powers and Murray[111] present a case of juvenile hypertension following unilateral pyelonephritis. The affected kidney was removed together with the major part of the adrenal. The blood pressure fell postoperatively but not to a normal level. The result of the cold pressor test returned to normal.

We have been rather disappointed with the effects of nephrectomy on hypertension in unilateral renal disease. The fact that one kidney is hypoplastic, contracted or functionless does not necessarily mean that its removal is followed by cure of the hypertension. Should the blood pressure begin to rise again, the patient, with hypertension and only one kidney, is in a less favorable position than before nephrectomy. It is our present impression that a bilateral splanchnic section should precede any nephrectomy; the latter operation might be tried if the splanchnic section has failed.

169. Atlas, L. N.: Lumbar Sympathectomy in the Treatment of Selected Cases of Peripheral Arteriosclerotic Disease, Am. Heart J. **22**:75 (July) 1941; Lumbar Sympathectomy in the Treatment of Peripheral Arteriosclerotic Disease: II. Gangrene Following Operation in Improperly Selected Cases, ibid. **23**:493 (April) 1942.

From the Lahey Clinic Bartels, Poppen and Richards [170] report on a series of 54 patients operated on for hypertension. Of these, 14 were operated on before 1935 and were not carefully selected. The operation before 1935 consisted of supradiaphragmatic splanchnicectomy and ganglionectomy. Nine of the 14 died during an average of twenty months after operation of causes related to hypertension. Four patients are still alive, but their blood pressure is just as high as before the operation. Another series of 41 patients operated on since 1935 was selected with definite criteria. They were under 40 years of age; their retinal vessels showed moderate sclerosis, and their hypertension was moderate to severe, with some fluctuation. They were subjected to a two stage subdiaphragmatic or transdiaphragmatic resection of the greater and the lesser splanchnic nerve and to the removal of the twelfth thoracic, the first lumbar and the second lumbar ganglion. The adrenal glands were visualized, and a biopsy specimen was taken from each kidney. If a sufficient amount of omentum was available, the left kidney was decapsulated and a nephro-omentopexy was carried out. Two deaths occurred after operation. Thirty-four per cent of the patients had a satisfactory drop in blood pressure; 26 per cent had a slight drop, and 39 per cent had no change at all. The average follow-up period was twenty-three months. Symptomatic improvement occurred in 71 per cent of patients, in spite of the fact that in half of them the blood pressure had not been altered. The authors feel that this high degree of symptomatic improvement justifies the operation, even though in only one third of the patients has the blood pressure been satisfactorily reduced.

Woods and Peet [171] took as the basis of their comparison cases reported by Wagener and Keith, in which five to nine year mortality statistics were available, and compared them with the mortality statistics of their seven years of follow-up records. In general, a favorable prognosis following operation seems to depend on the degree of retinal arteriolosclerosis. In the malignant phase the mortality was 99 per cent in the medical, and 33 per cent in the surgical, series after five years.

The hypertensive state was classified as early, moderate, marked and malignant (Keith-Wagener) in a series of 30 cases reported by de Takáts, Heyer and Keeton.[172] Of the various technical methods for

170. Bartels, E. C.; Poppen, J. L., and Richards, R. L.: Surgical Treatment of Hypertension (Results in Fifty-Four Cases), Lahey Clin. Bull. **2**:197 (Jan.) 1942.

171. Woods, W. W., and Peet, M. M.: The Surgical Treatment of Hypertension: II. Comparison of Mortality Following Operation with That of Wagner-Keith Medically Treated Control Series; a Study of Seventy-Six Cases, Five to Seven Years After Operation, J. A. M. A. **117**:1508 (Nov. 1) 1941.

172. de Takáts, G.; Heyer, H. E., and Keeton, R. W.: The Surgical Approach to Hypertension, J. A. M. A. **118**:501 (Feb. 14) 1942.

splanchnic nerve section, the transdiaphragmatic approach, consisting of the removal of the major splanchnic nerve from the fifth dorsal root to its entrance into the celiac ganglion and the excision of the ganglionated sympathetic trunk from the ninth dorsal to below the second lumbar ganglion, has given by far the best results and the only real reductions of high blood pressure. When such an operation was undertaken in various stages of hypertension, the degree of structural involvement determined the results. The malignant phase in a series of 8 cases has shown itself refractory to surgical treatment. The selection of cases of the early phase of the disorder and the employment of the extended splanchnic section, as described by Smithwick, seemed to be the important factors in obtaining good results. Outside of the actual lowering of blood pressure, which in turn may result in the diminution of the size of the heart and in improved electrocardiograms, an improvement in renal function, a marked postural hypotension with decrease in venous pressure and a decrease in reflex nervous irritability due to adrenal denervation have been observed. The latter may well be responsible for the symptomatic improvement, such as loss of headaches, palpitation and nervousness. In a few cases muscular implants into the kidney have been undertaken. The ultimate value of this procedure is still under scrutiny. The value of biopsy of the kidneys in predicting the results to be expected has become more and more clear as longer periods of observation have become available.

Grimson [173] reviews his previous experimental work, which tended to show that more might be accomplished by total paravertebral sympathectomy than by splanchnic nerve section. The renal type of experimental hypertension remains uninfluenced by total sympathectomy, but neurogenic hypertension does respond, at least for a time. In human beings the operation was carried out in three stages, two thoracic and one abdominal. At each thoracic operation the stellate ganglion, the thoracic sympathetic ganglionated chain, the entire splanchnic nerve and its branches and the major part of the celiac ganglion of the side in question are removed. The third stage, which is not always done, consists of bilateral lumbar sympathectomy down to or including the fifth lumbar ganglion. Eleven patients were operated on, 8 of whom had only the thoracic procedures. One death occurred after the first, and one after the second stage. The response of the patients varied from transient fall in pressure, followed by a restoration to almost the preoperative level, to relatively normal pressures over a period of fourteen months. The lowering of blood pressure occurring after this extensive sympathectomy must be due to a decrease of peripheral resistance, since cardiorenal functions remain unchanged.

173. Grimson, K. S.: Total Thoracic and Partial to Total Lumbar Sympathectomy and Celiac Ganglionectomy in the Treatment of Hypertension, Ann. Surg. **114**:753 (Oct.) 1941.

The author is careful in drawing any conclusions as to the lasting merit of this surgical procedure. It appears, however, to lower blood pressure more consistently than does splanchnic nerve section.

The correlation of the author's experimental studies with his carefully conducted clinical observations makes this one of the most valuable and sound contributions to the surgical treatment of hypertension. There is this to be said, however, before his surgical technic can be widely adopted, that the operation carries a definite mortality; it is more extensive and probably too severe for some patients, who would receive benefit from a less extensive procedure. Furthermore, by operating on patients with early stages of the disorder in the future less extensive operations may suffice, as shown by our own experience. Attention should also be called to the fact that renal and neurogenic hypertension may not be so readily differentiated in human beings. Possibly all renal pressor substances act through the vasomotor center.[174]

AMPUTATIONS

Schlossmann and Gerber[175] present a histologic study of 74 gangrenous extremities coming to amputation. The role of mural or intimal hemorrhage was emphasized as the most frequent factor precipitating acute thrombosis. A classification of arterial lesions which ultimately produced gangrene and necessitated amputation was given as follows:

Lesion	Percentage
Thrombosis secondary to hemorrhage	49
Thrombosis on a plaque	7
Massive hematoma of the wall	1
Arteriosclerosis	23
Occlusion by granulation tissue	20

A study of the atheroma, its capillarization and the state of its stroma showed that intimal hemorrhage was secondary to rhexis of the vascular channels traversing the necrotic atheroma. Intimal and medial capillarization in arteriosclerotic vessels were traced both to the lumen and to the vasa vasorum. No difference was found between vascular sclerosis in diabetic and that in nondiabetic persons.

The same conclusion regarding the lack of difference between diabetic and nondiabetic arteriosclerosis was reached by Lisa, Magiday and Hart.[176] Changes in the veins were different. Acute venous thrombosis of the larger radicals was encountered less frequently among

174. Dock, W.; Shidler, F., and Moy, B.: The Vasomotor Center Essential in Maintaining Renal Hypertension, Am. Heart J. **23**:513 (April) 1942.

175. Schlossmann, N. C., and Gerber, L.: Peripheral Arteriosclerosis, Ann. Surg. **115**:292 (Feb.) 1942.

176. Lisa, J. R.; Magiday, M., and Hart, J. F.: Peripheral Arteriosclerosis in the Diabetic and Nondiabetic, J. A. M. A. **118**:1353 (April) 1942.

diabetic patients, and the same was true of phlebosclerosis. Lymphangitis was encountered in the presence of infection, whether diabetes was present or not; pathologic changes in the nerves could not be demonstrated in either group. Dry gangrene occurred with frequency in both groups.

Macey and Bickel [177] present a ten year review of 264 amputations of lower extremities in patients with occlusive arterial disease The clinical diagnoses were thromboangiitis obliterans, arteriosclerosis obliterans with and without diabetes and acute arterial occlusion. In amputations through the thigh a long anterior and a short posterior flap was used. Alcohol or procaine hydrochloride was injected into the large nerves before they were severed. Below the knee a long posterior and a short anterior flap was used. The crest of the tibia was beveled and the fibula sectioned 1 to 2 inches (2.5 to 5 cm.) higher than the tibia. The wounds were all closed snugly except in the presence of lymphangitis or cellulitis. Gas gangrene was a potential complication in the presence of an open lesion with gangrene.

Twenty-five patients with thromboangiitis obliterans who were operated on below the knee had complications, with 22 reamputations; 3 patients had amputations through the thigh, with reamputation necessary in 1 case. One patient was operated on through the knee joint (Gritti-Stokes), and it was necessary to reamputate the leg above the knee. Of 63 patients without complications, amputation was through the lower part of the leg in 38, the thigh in 29 and the knee in 1.

Of 80 patients with arteriosclerosis obliterans without diabetes, postoperative complications developed in 22 and 13 died. Of the 13 who died, 12 had amputations through the thigh and 1 below the knee. The remaining 9 had difficulties with the stump healing, and 6 patients had to have reamputations.

Of 61 patients suffering from arteriosclerosis with diabetes, 18 had complications due to impaired circulation, sloughing or infection in the stump and 2 had gas gangrene. Seven of these 20 patients died.

Of the 16 patients with acute arterial occulsion, 4 died. These had associated diseases, 3 having rheumatic cardiac lesions. Fifteen amputations were done through the thigh, and 1 disarticulation was done through the hip joint. The popliteal artery was occluded in 10 patients, the femoral artery in 5 and the posterior tibial artery in 1. In 9 of the 16 patients the postoperative course was uneventful; in 2 patients healing was delayed. In another patient reamputation was required. Acute arterial occlusions seemed to be more frequent on the right side.

The number of reamputations and the poor results of amputations through the lower portion of the leg are the two striking features of this

177. Macey, H. B., and Bickel, W. H.: Amputation of Lower Extremities in Occlusive Arterial Diseases: A Ten-Year Review, Surg., Gynec. & Obst. **74**:821 (April) 1942.

review. It is our belief that a close study of the level of circulatory insufficiency minimizes the necessity for reamputations. It is also our impression that flapless amputations of the lower portion of the leg show a much larger percentage of primary union than the method used by the authors. Also, amputations following acute arterial occlusions should not be delayed until demarcation occurs.

Amputation of gangrenous parts by a necrotizing chemical agent is described by Mohs, Sevringhaus and Schmidt.[178] This chemical escharotic stimulates the development of an exceptionally healthy, highly vascular and germ-resistant granulation tissue. The technic used is to surround the gangrenous part with this fixative, which consists of a 40 per cent concentration of zinc chloride in a plastic base and which is applied about 2 mm. thick for twenty-four hours. There is no pain or bleeding, and the patient may walk around during the healing. The necrotic tissue is always cut through fixed tissue. Of a series of 66 cases, complete separation and healing occurred in 60.6 per cent. Failure in 10 cases was due to incomplete separation of the basal layer. In 6 cases there was extension of the gangrene; in 4 cases the patients signed their releases before completion of treatment, and in 4 cases the patients died of intercurrent diseases before healing occurred. No deaths were attributed to this procedure, and no breakdown of the scar occurred once healing took place.

The criteria which seemed to offer a favorable response to this treatment were (1) diabetic gangrene, for which the prognosis is better than for senile arteriosclerosis; (2) young patients, for whom the outlook is better; (3) patients showing good demarcation, in whom the response is better; (4) evidence of good reaction from living tissue; (5) strong pulsation of pedal arteries, and (6) good histamine flares on the foot. A high degree of arteriosclerosis offered a poor prognosis.

If this method proves to be successful in other series of cases, much will have been accomplished for a large group of elderly arteriosclerotic patients, in whom gangrenous toes with intractable pain necessitate a major amputation. Most of these patients are too feeble and too poor to hope for rehabilitation. The method certainly deserves trial, and further reports will be awaited with interest.

6 North Michigan Boulevard.

122 South Michigan Boulevard.

303 East Superior Street.

Michael Reese Hospital.

178. Mohs, F. E.; Sevringhaus, E. L., and Schmidt, E. R.: Conservative Amputation of Gangrenous Parts of Chemosurgery, Ann. Surg. **114**:274 (Aug.) 1941.

News and Comment

American Association for the Advancement of Oral Diagnosis.—The ninth annual congress of the American Association for the Advancement of Oral Diagnosis will be held in Boston November 12 and 13 at the Forsyth Dental Infirmary.

The subject of this year's congress will be 'The Military Aspects of Oral Diagnosis."

Members of the medical and the dental profession in the United States and the countries of the Western Hemisphere who are interested are cordially invited to attend and may obtain programs by communicating with the secretary, H. Justin Ross, 515 Madison Avenue, New York.

Federation Proceedings.—The Federation of American Societies for Experimental Biology, composed of the American Physiological Society, the American Society of Biological Chemists, the American Society for Pharmacology and Experimental Therapeutics, the American Society for Experimental Pathology, the American Institute of Nutrition and the American Association of Immunologists, has begun (1942) the publication of the *Federation Proceedings.*

Four issues will be published annually. Each year the March issue will contain the complete federation program of the scientific sessions of all the component societies as prepared for the forthcoming annual meeting, with abstracts of all scientific papers to be presented; the June and September issues will contain the full text of twenty or more papers presented at the annual meeting, including probably the papers on the joint society program and papers of several society symposiums; the December issue will contain material pertinent to the federation membership, i. e., the names of the officers and the membership list, together with an index of the completed volume.

The subscription price is $4 ($4.75 foreign), payable in advance. Subscriptions should be sent to Dr. D. R. Hooker, Managing Editor, 19 West Chase Street, Baltimore, Md.

Book Reviews

A Manual of Pharmacology and Its Applications to Therapeutics and Toxicity. By Torald Sollmann, M.D. Sixth edition. Price, $8.75. Pp. 1,298. Philadelphia: W. B. Saunders Company, 1942.

The sixth edition of this book on pharmacology is welcomed. The plan of this edition conforms to that of the fifth. The material is presented as before, so that the manual can be useful as a book for students and as a reference volume. The important general information of interest to students is presented in large type, while experimental details are printed in fine type. The author continues to increase the use of English terminology, although Latin terms are also given. This edition is larger than the preceding one. There is an extensive bibliography at the end of the book.

The reviewer considers it unfortunate that the author has not included a section on vaccines and serums. This certainly is an important aspect of pharmacology and therapeutics. The use of such agents is not only important during peacetime but is extremely important at present, when so many people from many sources are being congregated. Again, with a right increase in the emphasis on the prevention of disease in therapeutics, there is a need for greater emphasis on prophylaxis in textbooks on pharmacology. The section on the sulfanilamide compounds is well, but too briefly, presented. A more complete discussion is indicated when one realizes the extent to which these drugs are being employed by physicians throughout the world. The significance of these criticisms should not be overemphasized. The volume continues to be excellent and is recommended highly for a concise and crisp discussion of therapeutic agents.

The Eye Manifestations of Internal Diseases. By I. S. Tassman. Pp. 542, with 201 illustrations, including 19 in color. St. Louis: C. V. Mosby Company, 1942.

The reviewer was somewhat disappointed after seeing the title of this book to find many of the discussions of ocular manifestations of internal disease to be inadequate. He was unable to find in the index a reference to "vitamins" or to "riboflavin." Night blindness is dealt with in a line which says it may be due to lack of vitamin A. The discussion of progressive exophthalmos in relation to thyroid disease is not really adequate nor is the discussion of the ocular changes associated with renal disease. It is the reviewer's impression that this book is the work of an ophthalmologist who has made a good effort to deal with the ocular phases of internal disease but who could perhaps profit by collaboration with a well trained internist.

The Biology of the Negro. By Julian Herman Lewis. Price, $5. Pp. 433, with 17 tables. Chicago: The University of Chicago Press, 1942.

In clinics dealing with many Negro patients physicians are prone to make dogmatic statements about differences in the way disease manifests itself in Negroes and in white persons. That most of these popular views are not founded on actual fact is immediately obvious when one looks through Lewis' extraordinarily thorough and well documented book on every aspect of the anatomy, the biology and the disease characteristics of the Negro. Almost any disease can be found in the index, and reference to the pages dealing with it invariably yields a complete and satisfactory discussion. This contribution, of the first order, will be invaluable to all physicians, especially those working in southern clinics.

Dermatologic Therapy in General Practice. By Marion Sulzberger and Jack Wolf. Price, $5. Pp. 632, with 67 figures and 25 tables. Chicago: The Year Book Publishers, Inc., 1942.

This highly practical book by well known specialists in dermatology seems to fill the needs of a general practitioner in connection with cutaneous disease. There are many excellent illustrations and large numbers of prescriptions for lotions, salves, etc. Physical therapy and irradiation therapy are also adequately dealt with.